

Neuroplasticity of Dopamine Circuits After Exercise: Implications for Central Fatigue

Teresa E. Foley · Monika Fleshner

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Abstract Habitual exercise increases plasticity in a variety of neurotransmitter systems. The current review focuses on the effects of habitual physical activity on monoamine dopamine (DA) neurotransmission and the potential implication of these changes to exercise-induced fatigue. Although it is clear that peripheral adaptations in muscle and energy substrate utilization contribute to this effect, more recently it has been suggested that central nervous system pathways “upstream” of the motor cortex, which initiate activation of skeletal muscles, are also important. The contribution of the brain to exercise-induced fatigue has been termed “central fatigue.” Given the well-defined role of DA in the initiation of movement, it is likely that adaptations in DA systems influence exercise capacity. A reduction in DA neurotransmission in the substantia nigra pars compacta (SNpc), for example, could impair activation of the basal ganglia and reduce stimulation of the motor cortex leading to central fatigue. Here we present evidence that habitual wheel running produces changes in DA systems. Using *in situ* hybridization techniques, we report that 6 weeks of wheel running was sufficient to increase tyrosine hydroxylase mRNA expression and reduce D2 autoreceptor mRNA in the SNpc. Additionally, 6 weeks of wheel running increased D2 postsynaptic receptor mRNA in the caudate putamen, a major projection site of the SNpc. These results are consistent with prior data suggesting that habitually physically active animals may have an enhanced ability to increase DA synthesis and reduce D2 autoreceptor-mediated

inhibition of DA neurons in the SNpc compared to sedentary animals. Furthermore, habitually physically active animals, compared to sedentary controls, may be better able to increase D2 receptor-mediated inhibition of the indirect pathway of the basal ganglia. Results from these studies are discussed in light of our understanding of the role of DA in the neurobiological mechanisms of central fatigue.

Keywords Wheel running · Plasticity · Brain-derived neurotrophic factor · Basal ganglia · Physical activity

Introduction

Exercise-induced fatigue is an acute impairment in performance that includes a decline in force capacity and the eventual inability to produce this force (Enoka and Stuart 1992). Until recently, most of the literature examining the origin of fatigue produced by physical activity focused on alterations distal to the neuromuscular junction in the muscle. The contribution of “central” factors or factors upstream of the neuromuscular junction was for the most part overlooked. Undoubtedly, changes within the muscle contribute to exercise-induced fatigue; however, it is unlikely that dysfunction in the muscle is the sole mechanism. Fatigue can occur, for example, in the absence of any apparent signs of muscle dysfunction (Stokes et al. 1988) or inadequate substrate availability within the muscle (Bailey et al. 1993), and is influenced by psychological factors such as mood, arousal, external motivation, and expectation of the task (Craig et al. 2005; Jacobs and Bell 2004; Nybo and Secher 2004; Rietjens et al. 2005). As such, fatigue is multifaceted and is influenced by both central and peripheral factors (Meeusen et al. 2006b; Nybo

T. E. Foley · M. Fleshner (✉)
Department Integrative Physiology, Center for Neuroscience,
Clare Small Building, University of Colorado-Boulder, Boulder,
CO 80309-0354, USA
e-mail: fleshner@colorado.edu

and Secher 2004). Given that the central nervous system (CNS) stimulates muscle contractions, it is likely that changes in the brain or spinal cord could alter neural drive to the neuromuscular junction, initiating the onset of fatigue. The contribution of central nervous systems factors in the reduction in voluntary activation of skeletal muscles during physical activity has been termed “central fatigue” (Gandevia 2001). The current review will first describe several potential neural mechanisms of central fatigue, with a focused discussion on the role of DA neurotransmission. Secondly, we will examine the impact of habitual voluntary wheel running on DA basal ganglia pathways and hypothesize how plastic changes in the DA neurocircuitry may contribute to delayed exercise-induced fatigue found in habitually physically active rats.

Central Factors Involved in the Mechanisms of Fatigue

A reduction in voluntary activation of skeletal muscles during physical activity could occur at several levels of the CNS from the motor cortex down to the neuromuscular junction, and alterations in CNS pathways “upstream” of the motor cortex could contribute to exercise-induced fatigue (Gandevia et al. 1995, 1996). For example, there is evidence that changes in cerebral metabolism (Nybo and Rasmussen 2007; Nybo and Secher 2004), hyperthermia (Meeusen 2006b; Nielsen and Nybo 2003; Todd et al. 2005), sense of effort (Enoka and Stuart 1992), motivation (Burgess et al. 1991; Davis and Bailey 1997), ammonia accumulation (Guezennec 1998; Nybo et al. 2005), or monoamine neurotransmission (Bailey et al. 1993a; Meeusen 2006b; Newsholme et al. 1987) may be mechanistically linked to exercise-induced fatigue. Although each of these theories is important for explaining the contribution of the brain to central fatigue, we will focus our review on the role of monoamine neurotransmission, with a brief introduction to serotonergic systems and a more detailed description of dopaminergic systems (DA).

Brief Review of the Role of Monoamines in Central Fatigue

Substantial progress has been made toward identifying the potential mechanisms by which alterations in the neurotransmitter serotonin (5-HT) can influence central fatigue. Acworth et al. (1986) and Newsholme et al. (1987) were the first to suggest that elevations in the brain 5-HT could contribute to exercise-induced fatigue (Acworth et al. 1986; Newsholme et al. 1987). Because an increase in 5-HT can result in sleep (Jacobs 1991; Jacobs and Fornal 1999), it was hypothesized that an increase in 5-HT could

also cause a decrease in mental alertness and/or fatigue (central fatigue) (Newsholme et al. 1987). The proposed “central fatigue hypothesis” has opened up a new window in the study of exercise-induced fatigue and has been extensively studied to date (for the most recent reviews on the role of 5-HT in central fatigue see Blomstrand 2006; Fernstrom and Fernstrom 2006; Meeusen et al. 2006a, b; Newsholme and Blomstrand 2006).

Although there is overwhelming evidence for the involvement of 5-HT in central fatigue, it has become clear that the function of monoamines in the mechanism of exercise-induced fatigue is much more complex than originally hypothesized. One limitation of the hypothesis is the assumption that only one neurotransmitter, 5-HT, can influence fatigue. This complexity is best exemplified by the observation that drugs that alter the concentrations of DA (Bhagat and Wheeler 1973a, b; Bracken et al. 1988, 1989; Cooter and Stull 1974; Derevenco et al. 1981, 1982, 1986; Gerald 1978; Heyes et al. 1985; Kalinski et al. 2001; Meeusen et al. 1997a; Snider et al. 1983; Trudeau et al. 1990; Williams and Thompson 1973), nitric oxide (Lacerda et al. 2006), norepinephrine (Jacobs and Bell 2004), adenosine (Davis et al. 2003), and gamma-aminobutyric acid (GABA) (Abdelmalki et al. 1997) can also influence fatigue. For example, administration of baclofen, a GABA_B receptor agonist, can delay the onset of fatigue (Abdelmalki et al. 1997), while 5'-*N*-ethylcarboxamidoadenosine, an adenosine receptor agonist, can hasten the onset of fatigue (Davis et al. 2003) in rats. Consequently, to suggest that 5-HT by itself limits performance would be elementary. In fact, dysregulation of 5-HT can influence other neurotransmitters, such as DA, during exercise to fatigue.

Role of Dopamine in Central Fatigue

Dopamine Neurotransmission During Physical Activity and the Revised Central Fatigue Hypothesis

Dopamine is a member of the catecholamine family of neurotransmitters whose cell bodies are located in the pars compacta region of the substantia nigra (SNpc; or A9 region), an area implicated in the initiation of movement (Freed and Yamamoto et al. 1985; Meeusen et al. 2001). One of the most consistent findings in the animal literature is the observation that DA content and release is increased during physical activity. Bliss and Ailion (1971) were the first to report that male mice subject to 1 h of swimming at 37°C or 30 min of spontaneous running demonstrated an increase in brain DA and homovanillic acid (a DA metabolite) content in whole brain homogenates taken immediately after exercise (Bliss and Ailion 1971). The increase in DA content and release during physical activity

was later restricted to areas rich in DA innervation including the striatum (Bailey et al. 1992, 1993b, Freed and Yamamoto 1985; Hattori et al. 1994; Heyes et al. 1988; MacRae et al. 1987; Meeusen et al. 1997b; Sabol et al. 1990; Speciale et al. 1986; Wilson and Marsden 1995), midbrain (Bailey et al. 1992, 1993b, Chaouloff et al. 1987), hippocampus (Bailey et al. 1992, Chaouloff et al. 1987), brain stem (Blomstrand et al. 1989; Heyes et al. 1988), hypothalamus (Bailey et al. 1993b; Blomstrand et al. 1989; Chaouloff et al., 1987; Hasegawa et al. 2000; Heyes et al. 1988), spinal cord (Gerin et al. 1995; Gerin and Privat 1998), and cerebrospinal fluid (Chaouloff et al. 1986). Interestingly, the increase in DA during exercise is dependent on the speed and postural direction of the animal (Freed and Yamamoto 1985; Hattori et al. 1994), yet is increased independent of training status (trained versus untrained) (Blomstrand et al. 1989, Chaouloff et al. 1987; Lim et al. 2001; Meeusen et al. 1997b; Sabol et al. 1990), mode of exercise (swim versus treadmill versus wheel run) (Bliss and Ailion 1971; Elam et al. 1987; Hoffmann et al. 1994; Speciale et al. 1986), duration of exercise bout (20 min versus 60 min) (Bailey et al. 1993b; Chaouloff et al. 1986; Freed and Yamamoto 1985; Heyes et al. 1988), or sex of the animal (male versus female) (Bailey et al. 1992; Blomstrand et al. 1989). In contrast, the only human study to examine DA during physical activity reported no differences in striatal DA release 5–10 min post-vigorous running, as detected by positron emission tomography (PET) scans (Wang et al. 2000). However, because we cannot make definitive conclusions from only one PET study, the dynamics of DA neurotransmission during physical activity in humans requires further investigation.

Mark Davis, Steven Bailey, and colleagues have extended the original central fatigue hypothesis to account for the important interaction of 5-HT and DA during physical activity (Bailey et al. 1993a; Davis 1995; Davis et al. 2000; Davis and Bailey, 1997). Similar to DA, 5-HT neurotransmission is increased during physical activity in various brain areas of the rat (for excellent reviews see Struder and Weicker 2001a, b). Unlike DA, however, 5-HT content peaks at the onset of fatigue, while DA content is similar to resting levels at fatigue (Bailey et al. 1993). Davis and colleagues speculated that the increase in 5-HT activity during physical activity might contribute to fatigue through inhibition of the DA system. This hypothesis was later confirmed by pharmacological data suggesting that administration of a general 5-HT agonist (quipazine dimaleate; 1 mg/kg, i.p.) blocked the exercise-induced increase in DA, whereas administration of a 5-HT_{1C/2} antagonist (LY 53857; 1.5 mg/kg, i.p.) prevented the decrease in DA and its metabolite at exhaustion (Bailey et al. 1993). Based on this observation, Davis's "revised central fatigue hypothesis"

suggests that a low ratio of 5-HT:DA in the brain favors improved performance, whereas a high ratio of 5-HT:DA favors decreased performance (or central fatigue) (Davis and Bailey 1997).

While it is clear that changes in 5-HT can influence DA neurotransmission during exercise to fatigue, there are still several important unanswered questions regarding the role of DA in central fatigue. For example, the precise mechanisms for how a reduction in brain DA could impair exercise performance and influence central fatigue are currently unknown. Given the well-defined role of DA in the initiation of movement (Chaudhuri and Behan 2000; Marshall and Berrios 1979), it is plausible to suggest the brain contributes to central fatigue by altering dopaminergic circuits involved in movement. Additionally, it is likely that habitual physical activity influences exercise capacity by prolonging DA neurotransmission in these areas. The following two sections will provide support for the role of DA in central fatigue by providing specific mechanisms by which reduced DA neurotransmission can affect movement. This is followed by a brief discussion of some of the methods employed by researchers to augment DA activity during exercise to fatigue.

Role of Dopamine in Movement and Activation of the Basal Ganglia

Dopamine release from the SNpc is necessary for activation of the basal ganglia, a collection of midbrain neurons responsible for the initiation of movement (Chaudhuri and Behan 2000). The basal ganglia consist of four principal nuclei: the SN, caudate putamen (CPU), globus pallidus (GP), and the subthalamic nucleus (STN). Activation of DA cell bodies in the SNpc leads to intense release of DA into the CPU which gives rise to two major outputs responsible for motor control: the direct pathway which facilitates motor activity and the indirect pathway which inhibits motor activity. Dopamine has an overall stimulatory role in movement, as DA binding to D1 receptors in the CPU facilitates activation of the direct pathway, whereas DA binding to D2 receptors in the CPU inhibits activation of the indirect pathway of the basal ganglia.

In the direct pathway, D1 receptors are excitatory receptors located on GABAergic medium spiny neurons that co-express Substance P and dynorphin, and project to the pars reticulata region of the SN (SNpr) and internal segment of the GP (GPi) (Adell and Artigas 2004; Le Moine et al. 1991; Lu et al. 1998). If DA binds to D1 receptors expressed on GABAergic neurons in the CPU, then GABAergic neurotransmission to the SNpr/GPi complex is enhanced. This would lead to greater inhibition of GABAergic neurons in the SNpr/GPi complex, and

hence, disinhibition of glutamatergic neurons in the thalamus. Consequently, upon stimulation, activation of glutamatergic neurons in the thalamus will stimulate other glutamatergic neurons in the motor cortex that initiate movement (Chaudhuri and Behan 2000).

In contrast, in the indirect pathway, D2 receptors are inhibitory receptors located on GABAergic medium spiny neurons which co-express enkephalin and project to the external segment of the GP (GPe) (Adell and Artigas 2004; Le Moine et al. 1991; Lu et al. 1998). If DA binds to GABAergic neurons in the CPU, then GABAergic neurotransmission to the GPe would be reduced. This would lead to less inhibition of GABAergic neurons of the GPe, and an increase in GABA release to the STN. Here GABA will inhibit activation of glutamatergic neurons in the STN, which in turn will lead to less activation of GABAergic neurons in the SNpr/GPi complex. By removing activation of GABAergic neurons in the SNpr/GPi complex, upon stimulation, glutamate neurons in the thalamus will activate other glutamate neurons in the motor cortex to facilitate activation of the motor cortex and movement (Chaudhuri and Behan 2000). In summary, DA binding to CPU D1 receptors facilitates movement by activating the direct pathway of the basal ganglia, while DA binding to CPU D2 receptors facilitates movement by inhibiting activation of the indirect pathway of the basal ganglia. For a schematic diagram illustrating the effect of DA on the basal ganglia pathways refer to Fig. 1.

A disruption in DA neurotransmission in the SNpc, as seen in Parkinson's disease (Elsworth and Roth 1997), has deleterious effects on movement, fatigue, and activation of the basal ganglia. Indeed, complete ablation of catecholaminergic neurons in this area by the neurotoxin 6-hydroxydopamine (6-OHDA) has been shown to impair exercise performance to fatigue in a rat (Derevenco et al. 1978, 1981, 1982, 1986; Heyes et al. 1985; Trudeau et al. 1990). Furthermore, blockade of D2 receptors by raclopride (Hillegaart and Ahlenius 1987; Hillegaart et al. 1987) or haloperidol (Ahlenius and Hillegaart 1986; Ahlenius et al. 1984; Hillegaart et al. 1987) suppresses treadmill locomotion, potentially by removing D2-mediated inhibition of the indirect pathway of the basal ganglia. Collectively, these results suggest that a disruption in DA neurotransmission in the SNpc and CPU may be involved in the mechanisms by which reduced DA concentrations contribute to the central fatigue.

Manipulations that Increase Dopaminergic Activity During Exercise to Fatigue

Because DA is hypothesized to be critically involved in movement, a decrease in DA neurotransmission during

physical activity would hasten the onset of fatigue, while an increase in DA neurotransmission would be sufficient to delay the onset of fatigue. In fact, even before the introduction of the revised central fatigue hypothesis, attempts have been made to prolong DA neurotransmission during exercise to fatigue. Manipulations that increase DA synthesis (Avraham et al. 2001; Chinevere et al. 2002; Marshall and Berrios et al. 1979; Meeusen et al. 1997a; Struder et al. 1998; Sutton et al. 2005), stimulate extracellular DA release (Bhagat and Wheeler 1973a, b; Cooter and Stull 1974; Gerald 1978; Kalinski et al. 2001; Williams and Thompson 1973), inhibit DA reuptake (Bhagat and Wheeler 1973; Bracken et al. 1988, 1989; Snider et al. 1983), or directly activate DA neurons and/or DA receptors (Burgess et al. 1991; Heyes et al. 1985) are just some of the methods employed by researchers to prolong the increase in DA during exercise to fatigue. Some of these manipulations have been successful in impacting exercise-induced fatigue, while others have not.

For example, manipulations of tyrosine and dihydroxyphenylalanine (Dopa) availability are just one tool used by researchers to increase DA synthesis during exercise to fatigue. Because DA cannot readily cross the blood brain barrier, neurons must synthesize DA themselves. Dopamine synthesis is dependent on the availability of its precursor amino acid tyrosine (Milner and Wurtman 1987). Tyrosine must compete with other amino acids for entry into the brain, including tryptophan (the precursor to 5-HT) and the branch chain amino acids (isoleucine, leucine, valine), as they are mediated by the same carrier system (Oldendorf and Szabo 1976; Pardridge 1977). After entry into terminal region of the neuron, the rate-limiting enzyme tyrosine hydroxylase (TH) oxidizes tyrosine to form Dopa. Dopa is later decarboxylated by the enzyme aromatic-L-amino-acid decarboxylase to form DA.

An increase in brain tyrosine and/or Dopa availability could potentially increase DA synthesis during exercise to fatigue (Meeusen et al. 1997a). (A similar mechanism is proposed for tryptophan, the precursor of 5-HT (News-holme et al. 1987).) However, unlike tryptophan hydroxylase, the brain levels of TH are saturated with substrate under normal conditions (Agharanya and Wurtman 1982), and therefore, any attempt to "tyrosine load" the transport pump cannot produce significant increases in catecholamine synthesis (McTavish et al. 1999). This is confirmed by results showing no improvement in exercise performance to fatigue with tyrosine loading (Chinevere et al. 2002; Struder et al. 1998; Sutton et al., 2005). In addition, levodopa, a synthetic DA precursor that readily penetrates the blood brain barrier and bypasses the rate-limiting enzymatic step of DA synthesis (Yee et al. 2001), has no effect on exercise performance to fatigue in healthy subjects (Meeusen et al. 1997a). These results suggest that

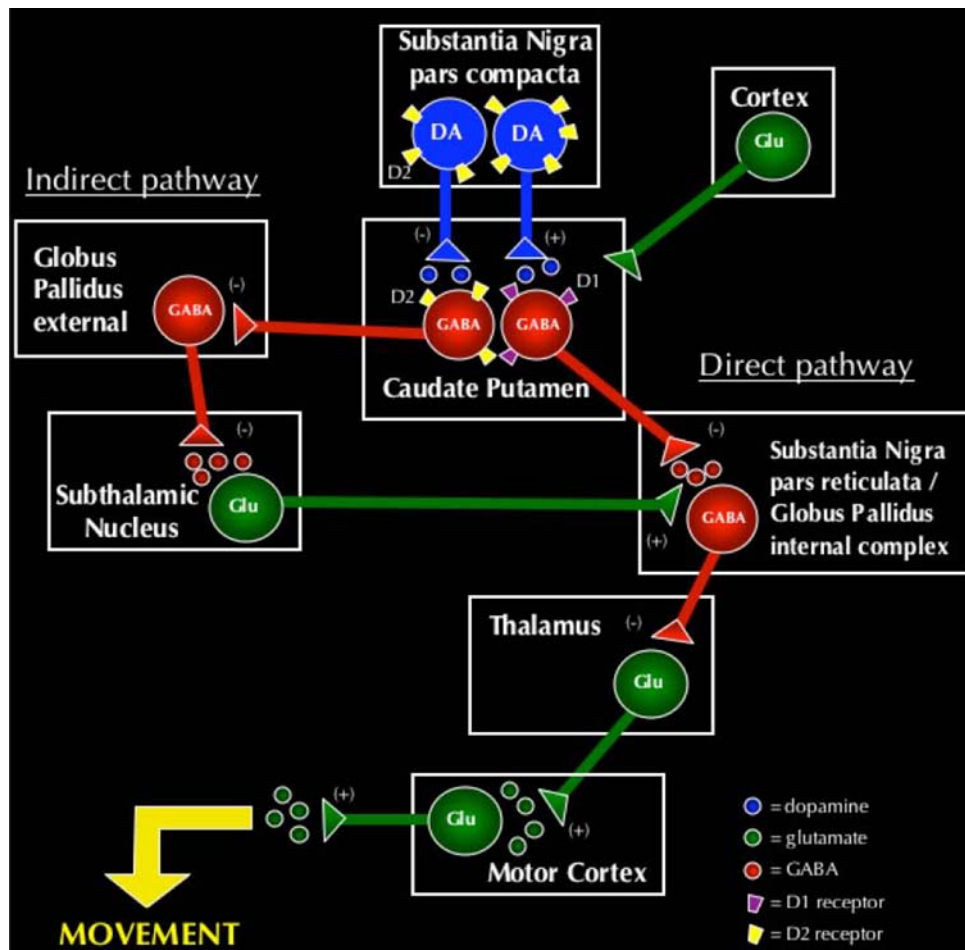


Fig. 1 Schematic diagram illustrating the effect of dopamine on basal ganglia pathways. Activation of substantia nigra pars compacta DA neurons leads to intense release of DA in the caudate putamen. If DA binds to D1 receptors expressed on GABAergic neurons in the caudate putamen, then GABAergic neurotransmission to the substantia nigra pars reticulata/globus pallidus internal complex is increased. This will lead to greater inhibition of GABAergic neurons in the substantia nigra pars reticulata/globus pallidus internal complex, and disinhibition of glutamatergic neurons in the thalamus. Here glutamate will stimulate other glutamate neurons in the motor cortex to initiate movement. If DA binds D2 receptors expressed on GABAergic neurons in the caudate putamen, then GABAergic

neurotransmission to the globus pallidus external will be reduced. This will lead to less inhibition of GABAergic neurons in the globus pallidus external, and an increase in GABA release to the subthalamic nucleus. Here GABA will inhibit activation of glutamatergic neurons in the subthalamic nucleus, which in turn will lead to less activation of GABAergic neurons in the substantia nigra pars reticulata/globus pallidus internal complex. By removing activation of GABAergic neurons in the substantia nigra pars reticulata/globus pallidus internal complex, glutamatergic neurons in the thalamus will activate other glutamate neurons in the motor cortex and stimulate movement. Abbreviations: DA = dopamine; GABA = gamma-aminobutyric acid; Glu = glutamate

increasing DA synthesis through precursor loading is insufficient to affect exercise-induced fatigue.

As a final point, pharmacological manipulations of DA systems have also been used to prolong the increase in extracellular DA during exercise to fatigue. The CNS stimulants methamphetamine (Kalinski et al. 2001), cocaine (Bracken et al. 1988, 1989), methylphenidate (or Ritalin) (Bhagat and Wheeler 1973b; Snider et al. 1983), amphetamine (Bhagat and Wheeler 1973a, b; Cooter and Stull 1974; Gerald 1978; Kalinski et al. 2001; Williams and Thompson 1973), and caffeine (Davis et al. 2003; Kalmar and Cafarelli 2004; Lim et al. 2001) were the first drugs used to manipulate exercise performance to fatigue

through activation of the DA system. As expected, intraperitoneal or intracranial injections of methylphenidate (Bhagat and Wheeler 1973b, Snider et al. 1983), amphetamine (Bhagat and Wheeler 1973a, b; Gerald 1978), and caffeine (Davis et al. 2003; Kalmar and Cafarelli 2004; Lim et al. 2001) prior to exercise delayed fatigue in rats. In contrast, various doses of cocaine (Bracken et al. 1988, 1989) or methamphetamine (Kalinski et al. 2001) have been shown to hasten fatigue, potentially by increasing muscle glycogen depletion and blood lactate concentration (Bracken et al. 1988, 1989) or reducing DA concentration (Kalinski et al. 2001) during treadmill running. These results suggest that administration of certain CNS

stimulants (i.e., methylphenidate, amphetamine, or caffeine) is sufficient to delay central fatigue by increasing extracellular DA neurotransmission during physical activity.

Based on these studies, several statements can be made regarding the role of DA in central fatigue. First, a reduction in DA neurotransmission during exercise may contribute to the central fatigue by negatively affecting dopaminergic neurocircuits involved in movement. Second, some manipulations that maintain DA neurotransmission during physical activity are sufficient to delay fatigue. The remainder of this review will add support to the role of DA in central fatigue by reviewing the effects of habitual physical activity (i.e., treadmill training and voluntary wheel running) on the adaptability or plasticity of dopaminergic neurocircuitry involved in movement.

In addition to its established role in the initiation of movement, it is important to recognize that DA systems have also been implicated in the neurobiology of reward and motivation. Previous reports have demonstrated that voluntary wheel running is rewarding (Belke 1997; Iversen 1993; Lett et al. 2000). Rats will lever-press for access to a running wheel (Belke 1997; Iversen 1993) and can develop conditioned place preference to environments associated with the aftereffects of wheel running (Lett et al. 2000). Because repeated exposure to drugs of abuse or natural rewards can sensitize DA neurons of the mesolimbic pathway (Robinson and Berridge 1993, 2000), alterations in dopaminergic neurocircuitry in areas involved in reward and motivation could alter the desire to run during exercise to fatigue in physically active rats compared to controls. Indeed, we have preliminary data to suggest that habitual physical activity can alter dopaminergic neurocircuitry involved in motivation; however, a discussion of these results is well beyond the scope of this review.

Habitual Physical Activity Induces Plasticity of Dopaminergic Systems

It is well known that exercise training leads to peripheral and central adaptations that can contribute to the beneficial effects of physical activity. One result of habitual physical activity is an increase in endurance capacity resulting in delayed fatigue during maximal exercise testing. Using a rat model, we can study the central mechanisms involved in delaying time to fatigue during maximal exercise testing. Rats that have voluntary access to a running wheel for 6 weeks have an increase in endurance capacity. Specifically, physically active rats can run $\sim 3\times$ longer on a treadmill before reaching fatigue during a maximal exercise test compared to sedentary counterparts (Campisi et al.

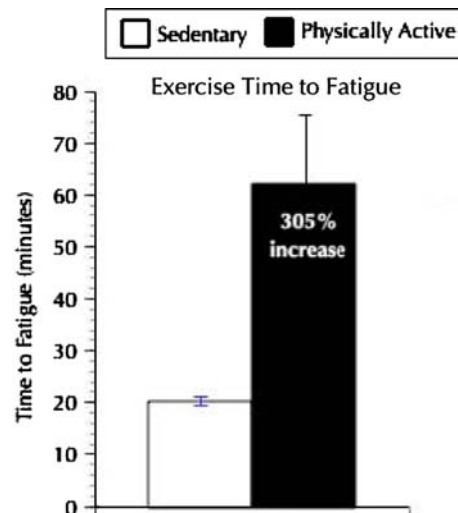


Fig. 2 Exercise time to fatigue (in minutes) of sedentary (\square ; $n = 5$) and physically active (\blacksquare ; $n = 5$) male F344 rats during treadmill testing. The exercise protocol to fatigue consisted of running on a motorized treadmill on a 10% grade at a speed of 17.5–20 m/min. Fatigue was defined as the inability to continue to run on the treadmill as observed as a failure to run after 10 consecutive foot shocks (1.6 mA). Physically active mean = 62.2 ± 13.3 min; sedentary mean = 20.4 ± 0.9 min, [$F(1,8) = 9.8, p = 0.01$]. Adapted from (Campisi et al. 2003)

2003) (Fig. 2). Based on the established role of DA in central fatigue, we hypothesize that habitual physical activity produces changes in dopaminergic neurocircuits involved in exercise-induced fatigue.

Dopamine neurons are subject to modulation by a variety of factors. Some of the factors involved in intrinsic regulation of central DA neurotransmission during physical activity include: TH, D1, and D2 receptors. Tyrosine hydroxylase is the rate-limiting enzyme in DA synthesis. D1 receptors are coupled to $G_{\text{stimulatory}}$ proteins that activate adenylyl cyclase to increase cAMP production from adenosine triphosphate. D1 receptors function primarily as postsynaptic heteroreceptors on non-dopaminergic neurons. In contrast, D2 receptors are coupled to $G_{\text{inhibitory}}$ proteins, and activation of D2 receptors leads to inhibition of adenylyl cyclase and a reduction in cAMP production. D2 receptors have dual roles in DA neurotransmission as autoreceptors and postsynaptic receptors. In the SNpc, D2 receptors act as somatodendritic inhibitory autoreceptors that limit local DA firing and release (Adell and Artigas 2004); while in DA projection sites, D2 receptors function as postsynaptic heteroreceptors on non-dopaminergic neurons.

Using in situ hybridization techniques, we were able to test the effect of 6 weeks of wheel running on the basal gene expression of factors capable of regulating DA neurotransmission during physical activity including TH, D1, and D2 receptors. Quantification of TH (300 bp), D1,

(460 bp) and D2 receptor (495 bp) messenger ribonucleic acid (mRNA) occurred at several levels and subdivisions of the SNpc and CPU of habitually physically active and sedentary male F344 rats ($n = 10/\text{group}$; Table 1).

Effect of Habitual Physical Activity on Dopaminergic Factors Involved in Movement

Alterations in DA-mediated stimulation of movement and the motor cortex may be involved in the mechanisms by which habitual physical activity delays central fatigue. It is well established that DA content increases and DA release occurs during 1–2 h of physical activity. Moreover, DA initiates movement through activation of the basal ganglia. Dopamine binding to CPU D1 receptors stimulates movement by activating the direct pathway of the basal ganglia, while DA binding to CPU D2 receptors stimulates movement by inhibiting activation of the indirect pathway of the basal ganglia. Consequently, it is possible that physically active rats may be better able to delay fatigue compared to sedentary counterparts by prolonging the increase in DA in the nigrostriatal pathway.

Tyrosine Hydroxylase mRNA Expression in Substantia Nigra Pars Compacta

Because TH is particularly susceptible to physiological regulation and pharmacological manipulation, an increase in rate-limiting TH availability in the presence of adequate tyrosine could potentially alter the amount of DA synthesis in the SNpc during physical activity. Indeed, increased TH expression has been shown to be a good predictor of increased DA synthesis (Elsworth and Roth 1997). Consistent with our hypothesis, preliminary data suggest that 6 weeks of wheel running significantly elevated basal levels of TH mRNA in the mid-SNpc [$F(1,17) = 7.196$; $p = 0.02$] and a trend for an increase in the caudal SNpc [$F(1,17) = 3.779$; $p = 0.07$] compared to sedentary controls (Fig. 3). Our results are consistent with a previous report that 24-month-old male F344 rats treadmill trained

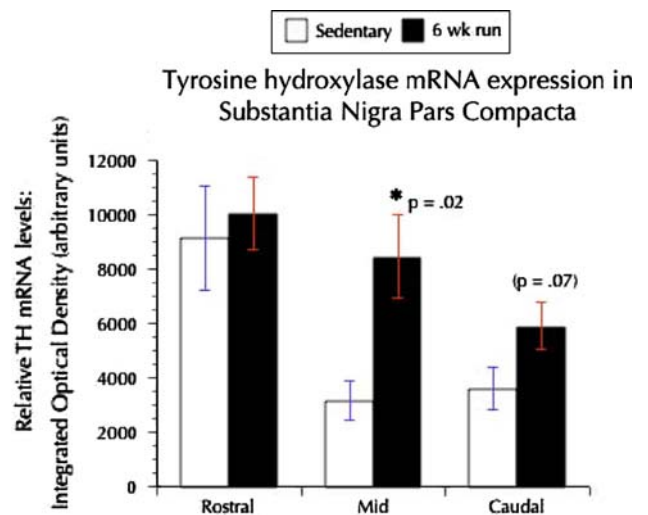


Fig. 3 Expression of tyrosine hydroxylase (TH) messenger RNA in the rostral to caudal subregions of the substantia nigra pars compacta of animals allowed access to a running wheel for 6 weeks (6 wk run ■; $n = 10$) or sedentary conditions (sedentary □; $n = 9$). Values represent mean integrated density \pm SEM. Fisher protected least significant difference: * $p < 0.05$ with respect to sedentary

for 5 days had increased TH mRNA in the SN (Tumer et al. 2001). Furthermore, using high-performance liquid chromatography techniques, Hattori (1994) demonstrated a 135–180% increase in striatal TH activity in rats trained to run on a treadmill at 18 m/min (Hattori et al. 1994). Collectively, these results suggest that alterations in TH gene expression, and potential DA synthesis, may contribute to differences in DA synthesis capacity between habitually physically active and sedentary animals.

D2 Autoreceptor mRNA Expression in Substantia Nigra Pars Compacta

Upon stimulation, D2 autoreceptors could potentially constrain DA activity during physical activity by increasing K^+ conductance (Adell and Artigas 2004) ultimately hyperpolarizing the cell. Compared to sedentary counterparts, however, physically active animals had significant reductions in basal D2 autoreceptor mRNA in the caudal

Table 1 Brain area and coordinates of factors examined in habitually physically active and sedentary rats

Brain area	Factors examined	Levels and coordinates	Subdivisions
Substantia nigra pars compacta	TH, D2 autoreceptor mRNA expression	–4.8 to –6.3 mm posterior to bregma	Rostral, mid, caudal
Caudate putamen	D1 and D2 postsynaptic mRNA expression	Rostral (2.2–0.7 mm anterior to bregma); mid (0.48 anterior to –0.8 mm posterior to bregma); caudal (–0.92 to –1.80 mm posterior to bregma)	Dorsolateral, dorsomedial, ventrolateral, ventromedial

Coordinates according to Paxinos and Watson (1998)

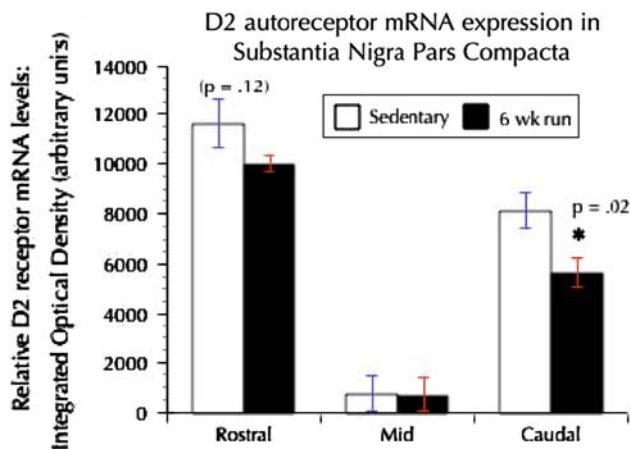


Fig. 4 Expression of dopamine receptor D2 messenger RNA in the rostral to caudal subregions of the substantia nigra pars compacta of animals allowed access to a running wheel for 6 weeks (6 wk run ■; $n = 10$) or sedentary conditions (sedentary □; $n = 9$). Values represent mean integrated density \pm SEM. Fisher protected least. Significant difference: $*p < 0.05$ with respect to sedentary

aspect of the SNpc [$F(1,17) = 6.759$; $p = 0.02$] and a trend for a reduction in the rostral SNpc [$F(1,17) = 2.663$; $p = 0.12$] (Fig. 4). If the reduction in D2 mRNA corresponds to a reduction in functional receptor expression, these data suggest that physically active animals could be better able to limit constraint of DA activity during physical activity by reducing local D2 autoinhibition of DA neurons in the SNpc. Furthermore, because the SNpc sends vast projections to the CPU (Francois et al. 1999), a reduction in D2 autoinhibition in this area could delay exercise-induced fatigue in physically active animals by increasing DA neurotransmission in this area.

D1 and D2 Postsynaptic Receptor mRNA Expression in Caudate Putamen

Alterations in D1 and D2 receptor gene expression during physical activity could also affect DA neurotransmission and activation of the motor cortex during exercise to fatigue. An increase in the expression of either the D1 or D2 receptors would stimulate movement by increasing activation of the direct pathway or increasing inhibition of the indirect pathway, respectively. Despite the similarities in D1 postsynaptic mRNA between groups (Fig. 5a), physically active animals demonstrated elevated basal levels of D2 postsynaptic mRNA throughout the CPU compared to sedentary controls [$F(1,17) = 22.276$; $p = 0.0002$] (Fig. 5b).

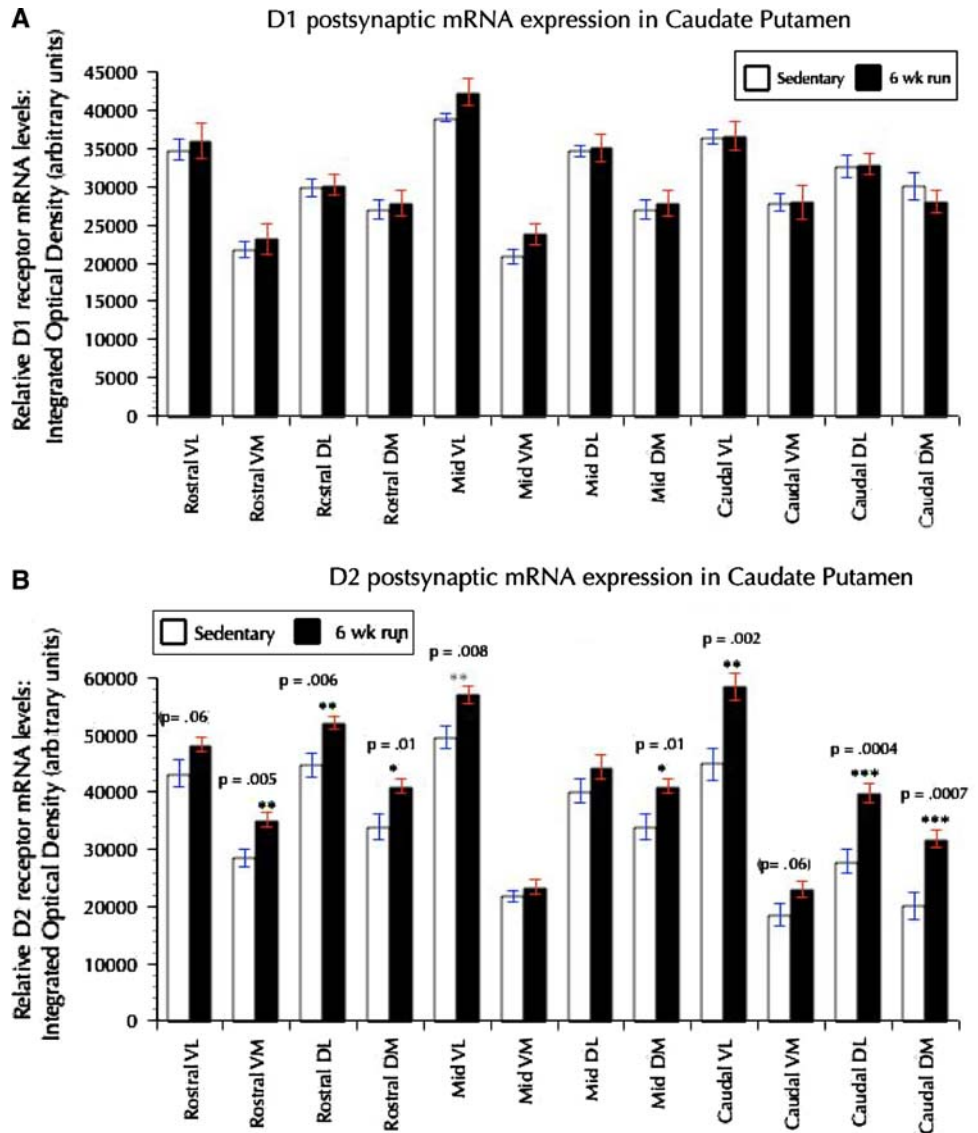
The increase in D2 mRNA of habitually physically active animals suggests that these animals may have an enhanced ability to inhibit activation of the indirect pathway of the basal ganglia compared to sedentary controls. The elevation of D2 mRNA after 6 weeks of wheel running

is consistent with prior reports examining [^3H]-spiperone receptor binding (a label of D2 receptor dynamics) in treadmill-trained rats (Gilliam et al. 1984; MacRae et al. 1987). Gilliam et al. (1984) reported that 12 weeks of interval (20 repeats, 54 m/min, 30 min) or endurance (27 m/min, 60 min) training was sufficient to elevate [^3H]-spiperone receptor binding in the striatum of treadmill-trained rats compared to control rats (Gilliam et al. 1984). This observation was confirmed in a second report demonstrating an increase in striatal [^3H]-spiperone receptor binding in young rats treadmill trained for 6 months compared to sedentary controls (MacRae et al. 1987). Taken together, these results suggest that (1) the increased levels of mRNA for D2 receptors likely result in an increase in D2 expression, and (2) alterations in D2 receptor expression may be involved in the mechanisms by which habitually physically active animals are better able to delay fatigue compared to sedentary controls.

At the level of D1 mRNA, it appears that 6 weeks of wheel running is insufficient to alter D1-receptor mediated activation of the direct pathway of the basal ganglia. However, because we only quantified basal mRNA expression in this study, it should be kept in mind that negative results (or no change in mRNA between groups) do not necessarily imply that the D1 receptor is not involved in the mechanisms by which habitual physical activity facilitates activation of direct pathway in the basal ganglia and delays fatigue. In fact, prior work in treadmill-trained rats has demonstrated that 7 days of intense treadmill running (36 m/min) is sufficient to induce c-Fos expression, a marker of neuronal activation, in the striatum compared to control conditions, and this increase is dependent upon activation of the D1 receptor (Liste et al. 1997). Additionally, another transcription factor, delta FosB, has been shown to be sensitive to the effects of habitual wheel running (Werme et al. 2002). Therefore, it is possible that 6 weeks of habitual wheel running may still be sufficient to alter D1 protein expression in the absence of changes in mRNA expression. The effect of habitual physical activity on the protein expression of factors capable of regulating DA neurotransmission warrants further investigation. The hypothesis for the mechanisms underlying the beneficial effect of habitual physical activity on DA factors involved in movement is depicted in Fig. 6.

In addition to the intrinsic regulators of DA neurotransmission presented here, a reduction in dopamine transporter (DAT) expression, a protein important in DA uptake, could also contribute to enhanced DA availability during physical activity. Recently, Petzinger et al. (2007) had reported that treadmill training is sufficient to alter DAT mRNA expression in midbrain DA neurons (Petzinger et al. 2007). Male mice subject to 28 days of intense treadmill training demonstrated a reduction in DAT mRNA

Fig. 5 Expression of dopamine receptor D1 (a) and D2 (b) messenger RNA in the rostral to caudal subregions of the caudate putamen of animals allowed access to a running wheel for 6 weeks (6 wk run ■; *n* = 10) or sedentary conditions (sedentary □; *n* = 9). Values represent mean integrated density ± SEM. Fisher protected least significant difference: **p* < 0.05, ***p* < 0.01, ****p* < 0.001 with respect to sedentary. Abbreviations: VL = ventrolateral, VM = ventromedial, DL = dorsolateral, DM = dorsomedial



in the SN compared to sedentary counterparts. In the same study, treadmill-trained rats, compared to sedentary controls, showed an increase in striatal DA levels (Petzinger et al. 2007). Taken together, these results suggest that downregulation of DAT expression is sufficient to increase synaptic DA availability in habitually physically active animals, and support our model that habitually physically active animals may be better able to delay fatigue compared to sedentary counterparts by prolonging the increase in DA in the nigrostriatal pathway.

Extrinsic Regulators of Dopaminergic Neurotransmission During Physical Activity

Although we have provided evidence that habitually physically active rats may be better able to intrinsically regulate

DA pathways involved in movement during exercise to fatigue compared to sedentary controls, there are several external regulators of DA neurotransmission that deserve mention. In addition to 5-HT, one external regulator of DA neurotransmission that has received a great deal of attention in studies investigating the positive effects of physical activity on cognitive function and brain “health,” but has received little attention in the mechanisms of central fatigue is brain-derived neurotrophic factor (BDNF). The neurotrophin BDNF, and its receptor tyrosine kinase B (TrkB), are highly expressed in DA midbrain neurons (Guillin et al. 2001); and BDNF has been shown to stimulate DA release (Beck et al. 1993; Hyman et al. 1991; Martin-Iverson et al. 1994; Spina et al. 1992) and enhance survival of DA neurons, including those that degenerate in Parkinson’s disease (Hyman et al. 1991). BDNF and TrkB are upregulated by voluntary exercise in the hippocampus (for review see

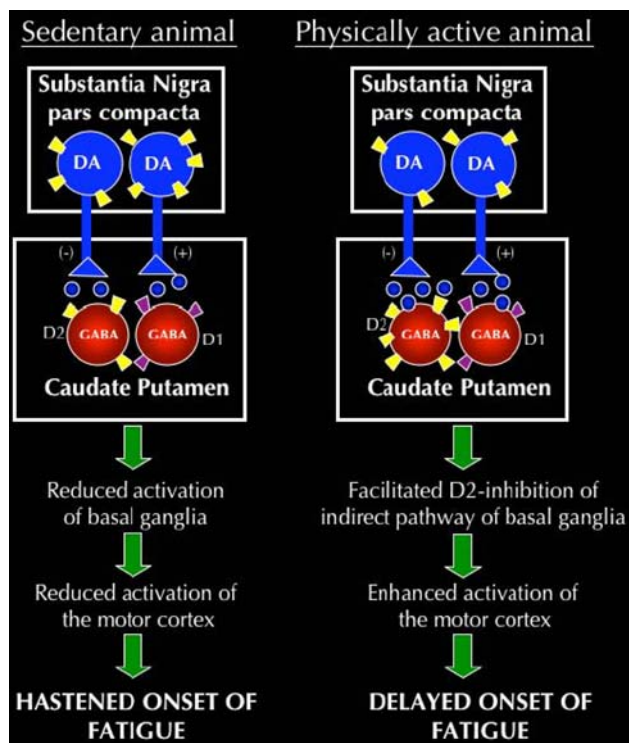


Fig. 6 Diagram of the effect of habitual physical activity on dopaminergic factors involved in movement. Habitually physically active animals, compared to sedentary counterparts, have an enhanced ability to increase dopamine (DA) synthesis in the substantia nigra pars compacta, as well as reduce D2 autoreceptor inhibition of DA neurons in the substantia nigra pars compacta. Because of the potential increase in DA release in the caudate putamen from the SNpc, habitually physically active animals may be better able to augment D2-mediated inhibition of the indirect pathway of the basal ganglia, leading to facilitated activation of the motor cortex and delayed fatigue compared to sedentary controls

Cotman and Berchtold 2002; Dishman et al. 2006; Russo-Neustadt and Chen 2005; Vaynman and Gomez-Pinilla 2005) and the ventral tegmental area (Van Hooymissen et al. 2003); and local administration of BDNF can increase locomotor activity in a sedentary rat (Altar et al. 1992; Horger et al. 1999; Martin-Iverson et al. 1994), presumably by activation of DA neurons.

Based on these findings, we hypothesize that exercise-induced increases in BDNF could contribute to the prolonged DA neurotransmission and the enhanced locomotor activity in physical active rats, and may be involved in the mechanisms by which habitual physical activity delays fatigue compared to sedentary controls. Although there is only one report examining BDNF levels during exercise to fatigue (Rojas Vega et al. 2006), the authors reported that serum BDNF transiently increased at fatigue in healthy male athletes compared to rest and recovery values. We have preliminary data to suggest that habitual physical activity alters BDNF expression in the SNpc. Animals allowed access to a running wheel for 6 weeks had

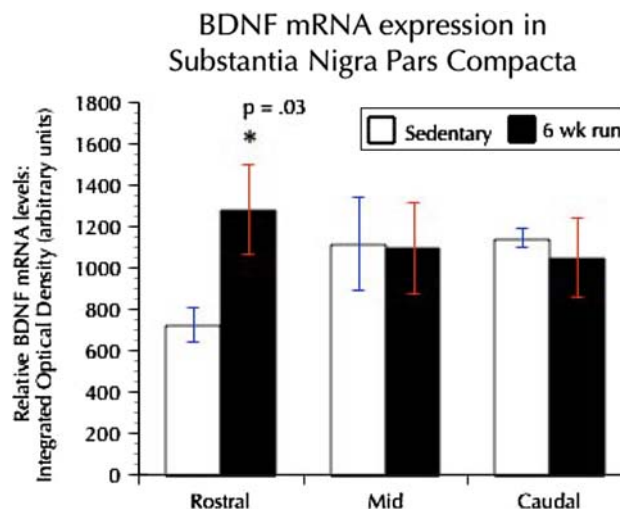


Fig. 7 Expression of brain-derived neurotrophic factor (BDNF) messenger RNA in the rostral to caudal subregions of the substantia nigra pars compacta of animals allowed access to a running wheel for 6 weeks (6 wk run ■; $n = 9$) or sedentary conditions □; $n = 9$). Values represent mean integrated density \pm SEM. Fisher protected least significant difference: * $p < 0.05$ with respect to sedentary

elevated BDNF mRNA expression in the rostral aspect of the SNpc [$F(1,16) = 5.782$; $p = 0.03$] compared to sedentary controls (Fig. 7). If the increase in BDNF mRNA translates into increased protein expression, these data suggest that enhancement of BDNF-mediated neuroplasticity of basal ganglia DA systems in physically active rats could lead to altered DA availability during physical activity and delayed exercise-induced fatigue when compared to sedentary rats.

These findings may also be important for the protective effect of exercise on dopamine-related neurodegenerative diseases such as Parkinson's disease. It is well established that physical activity has beneficial effects on Parkinson's disease in both the human (Chen et al. 2005; Crizzle and Newhouse 2006) and animal models (Howells et al. 2005; Tillerson et al. 2003). Furthermore, BDNF has been shown to increase the survival of DA neurons (Hyman et al. 1991). Therefore, it is possible that physical activity may reduce vulnerability of DA neurons in part by increasing BDNF availability and inducing BDNF-mediated plasticity of basal ganglia systems.

Conclusion

To our knowledge, this review is the first to provide specific mechanisms for how modulation of DA neurotransmission during physical activity could impair exercise performance and provide a mechanism for central fatigue. We hypothesize that disruption in DA neurotransmission in the SNpc would reduce activation of the basal ganglia and

the motor cortex leading to reduced neural drive to the skeletal muscles, and the onset of fatigue. In addition, we suggest that habitual physical activity delays fatigue by inducing plasticity in dopaminergic neurocircuits involved in movement. If our changes in mRNA do indeed translate into changes in functional protein expression and function, our data suggest that habitually physically active animals may have an enhanced ability to increase DA synthesis in the SNpc, and well as reduce D2 autoreceptor inhibition of DA neurons in the SNpc compared to sedentary animals. Furthermore, habitually physically active animals may be better able than sedentary animals to increase D2-mediated inhibition of the indirect pathway of the basal ganglia, leading to delayed fatigue.

These results are another example of the functionally important consequences of habitual exercise on the plasticity of central neural circuits. Here we present data that wheel running stimulates changes in basal ganglia DA systems, and these changes could have important implications for understanding the role of DA in central fatigue. The mechanisms for exercise-induced changes in DA systems remain unknown, although a role for BDNF is possible. By understanding the underlying neurobiological mechanisms involved in exercise-induced fatigue, novel pharmacological targets could be developed that delay fatigue during physical activity and reduce the experience of fatigue suffered by neurodegenerative disease patients.

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