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Central monoaminergic systems are a site of convergence of signals conveying the experience of exercise to brain circuits involved in cognition and emotional behavior

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Abstract

Physical activity can enhance cognitive function and increase resistance against deleterious effects of stress on mental health. Enhanced cognitive function and stress resistance produced by exercise are conserved among vertebrates, suggesting that ubiquitous mechanisms may underlie beneficial effects of exercise. In the current review, we summarize the beneficial effects of exercise on cognitive function and stress resistance and discuss central and peripheral signaling factors that may be critical for conferring the effects of physical activity to brain circuits involved in cognitive function and stress. Additionally, it is suggested that norepinephrine and serotonin, highly conserved monoamines that are sensitive to exercise and able to modulate behavior in multiple species, could represent a convergence between peripheral and central exercise signals that mediate the beneficial effects of exercise. Finally, we offer the novel hypothesis that thermoregulation during exercise could contribute to the emotional effects of exercise by activating a subset of temperature-sensitive serotonergic neurons in the dorsal raphe nucleus that convey anxiolytic and stress-protective signals to forebrain regions. Throughout the review, we discuss limitations to current approaches and offer strategies for future research in exercise neuroscience.

Key words: anxiety, norepinephrine, physical activity, serotonin, wheel running.

Introduction

It is now well established that the physical activity status of the organism impacts the structure and function of the nervous system, resulting in changes in associated behaviors (Cotman et al. 2007; Kramer & Erickson 2007; Gomez-Pinilla & Hillman 2013; Morgan et al. 2015). Physical activity status refers to the degree to which an organism engages in regular physical activity behaviors, whether these are for survival, fitness, or fun. Risk factors for a sedentary lifestyle are well documented, as are beneficial effects of regular physical activity. Taking center stage among the beneficial effects of physical activity are an enhancement of cognitive functions and an increase in stress resistance. In the current review, we will draw

from data obtained from a variety of vertebrates to briefly summarize the benefits of physical activity on cognitive function and stress resistance. Next, we will discuss signaling factors potentially involved in communicating the effects of exercise to the nervous system. Signaling factors considered will be both those initiated from the periphery during exercise, as well those originating from within the brain itself. Finally, we will summarize data consistent with the hypothesis that the monoamines norepinephrine (NE) and serotonin (5-HT) are a key point of convergence of peripheral and central signaling factors and are thus intimately involved in the mechanisms by which exercise enhances cognitive function and increases stress resistance.

Exercise Enhances Cognitive Function: Role of Growth Factors

The beneficial effects of physical activity on cognitive function have been extensively reviewed (Kramer & Erickson 2007; Gomez-Pinilla & Hillman 2013; Cassilhas et al. 2015; Fischer 2015; Hamilton & Rhodes 2015; Prakash et al. 2015). Physical activity can impact a wide variety of cognitive and learning processes including executive control (Hillman et al. 2003; Hillman et al. 2014), attentional processing (Budde et al. 2008; Medina et al. 2010), and spatial memory (Cassilhas et al. 2015). Although exercise is able to impact cognitive function in healthy individuals, physical activity is most beneficial in clinical populations. For example, physical activity can slow the cognitive decline associated with age (Kramer et al. 2006; Scherder et al. 2014), Alzheimer's disease (Yang & Coote 1998), Parkinson's disease (Murray et al. 2014; David et al. 2015), and after traumatic brain injury (Szabo 1994; Griesbach et al. 2009). Cognitive benefits of physical activity appear to be conserved in vertebrates and, in addition to humans, have been reported in nonhuman primates (Rhyu et al. 2010), rodents (van Praag et al. 1999a; Griffin et al. 2009), and zebra fish (Luchiani & Chacon 2013).

Exercise elicits structural plasticity in a wide variety of brain regions related to cognitive functions (Morgan et al. 2015). In the hippocampus, for example, exercise increases angiogenesis (Van der Borght et al. 2009), dendritic complexity (Redila & Christie 2006; Shih et al. 2013), spine density (Eadie et al. 2005), volume (Thomas et al. 2015), and adult neurogenesis (van Praag et al. 1999b; van Praag 2008). Growth factors seem to be especially important for mediating the cognitive and structural plasticity after exercise. Exercise increases circulating insulin-like growth factor-1 (IGF-1; Llorens-Martin et al. 2010), vascular endothelial growth factor (VEGF; Schobersberger et al. 2000), and brain-derived neurotrophic factor (BDNF; Coelho et al. 2013; but see Maass et al. 2015). These circulating growth factors can influence the brain directly (Carro et al. 2000). Indeed, several studies report that circulating BDNF (Trejo et al. 2001; Trejo et al. 2008) or IGF-1 (Duman et al. 2009) are important for the increase in neurogenesis and the antidepressant effects of exercise in animal models. Exercise also increases the synthesis of growth factors within the brain, including the hippocampus, cortex, and amygdala (Neeper et al. 1995; Neeper et al. 1996; Gomez-Pinilla et al. 1997; Ding et al. 2006; Greenwood et al. 2009). Blocking the function of BDNF with intra-hippocampal administration of an immunoadhesin chimera (TrkB-IgG) that mimics the BDNF receptor, TrkB, to selectively bind BDNF has been reported to prevent the enhancement of cognitive function produced by exercise in rats (Vaynman et al. 2004; Gomez-Pinilla et al. 2008). BDNF could also contribute to the increase in synaptic plasticity and neurogenesis noted after exercise (Poo 2001; Gomez-Pinilla et al. 2008; Ding et al. 2011; Park & Poo 2013), which together could contribute to beneficial effects of exercise (Bjornebekk et al. 2005; Clark et al. 2008; Duman et al. 2008; Marais et al. 2009; Fuss et al. 2010; Voss et al. 2013). Consistent with the rodent data are reports that humans with a prominent single-nucleotide polymorphism on the BDNF gene (BDNF Val66Met) display impaired learning and memory (Brooks et al. 2014; Montag et al. 2014). One particularly interesting potential role of adult hippocampal neurogenesis is the clearance of old memories in order to make way for new learning (Frankland et al. 2013). Akers et al. (2014) reported that mice allowed voluntary access to running wheels for 6 weeks after learning of contextual fear conditioning showed markedly weaker memory of the conditioning context compared with sedentary mice, and this forgetting was

dependent on the formation of new cells in the hippocampus (Akers et al. 2014). However, exercise-induced neurogenesis might elicit forgetting only under specific learning conditions. Greenwood et al. (2009) observed no evidence of exercise-induced loss of fear memories using a contextual fear conditioning protocol that resulted in high levels of fear in adult rats (Greenwood et al. 2009). Moreover, Mustroph et al. (2015) found that adult hippocampal neurogenesis was not necessary for wheel running to abolish the memory for cocaine conditioned place preference in mice (Mustroph et al. 2015).

Importantly, facilitation of adult neurogenesis and memory benefits from exercise seems to be conserved across vertebrate taxa. Zebra fish exercise trained by swimming against a current, for example, demonstrates enhanced learning of appetitive Pavlovian conditioning (Luchiani & Chacon 2013). European Starling bird exercise trained in a wind tunnel that mimics the birds' natural flight were reported to display enhanced neuronal recruitment in the telencephalon, which houses the birds' cerebral cortex, amygdala, and hippocampus, during flight compared with another group of birds that were not trained. The enhanced neuronal recruitment in the trained group was paralleled by an increase in neurogenesis in the telencephalon, as revealed by doublecortin immunohistochemistry (Hall et al. 2014). These data suggest that the increase in adult neurogenesis and associated memory benefits may be a conserved effect of exercise in vertebrates. To our knowledge, the effects of exercise on neural models of learning and memory in invertebrates have not been investigated. The characterization of an effective exercise training paradigm in *Drosophila* (Tinkerhess et al. 2012a) could provide convenient means with which to investigate the genetic and molecular mechanisms underlying the effects of exercise on learning. In fact, several weeks of exercise training slowed the age-related decline in climbing performance in *Drosophila*, an effect that was dependent on the presence of *spargel*, the invertebrate homolog of the vertebrate transcriptional co-activator PPAR- γ co-activator-1 α (PGC-1 α ; Tinkerhess et al. 2012b). This is especially interesting considering that muscle PGC-1 α drives the expression of a newly identified myokine, FNDC5 (Irisin; Bostrom et al. 2012), which has been reported to mediate the increase in hippocampal BDNF after exercise in mice (Wrann et al. 2013).

Exercise Increases Stress Resistance

In addition to enhancing cognitive function and learning and memory processes, physical activity is also well known to confer protection against deleterious effects of stress. The stress-buffering effects of exercise can be observed in a wide variety of stress responsive systems, including oxidative stress (Ozbeyli et al. 2015), attenuation of mild stress-induced increases in hypothalamic-pituitary-adrenal (HPA) axis activity (Droste et al. 2006; Greenwood et al. 2008; Campeau et al. 2010), facilitation of habituation of the sympathetic nervous system (Masini et al. 2005) and HPA axis (Sasse et al. 2008; Sasse et al. 2013) response to chronic stress, modulation of stress-induced monoaminergic signaling (Dishman 1997a; Dishman et al. 1997; Greenwood et al. 2003a; Greenwood et al. 2003b; Clark et al. 2015), and reduction in incidence and severity of stress-related psychiatric disorders such as depression (Babyak et al. 2000; Blumenthal et al. 2012), anxiety (Herring et al. 2010; Asmundson et al. 2013; Stonerock et al. 2015), and post-traumatic stress disorder (Newman & Motta 2007; Powers et al. 2015).

Interestingly, like the enhancement of cognitive function, exercise-induced stress resistance is conserved in vertebrates. For example, rats

allowed voluntary access to running wheels for 6 weeks are protected against stress-induced elevations in HPA axis activity (Droste et al. 2006; Greenwood et al. 2008; Campeau et al. 2010) and depression- and anxiety-like behavioral effects of exposure to a variety of laboratory stressors (reviewed in Greenwood & Fleshner 2011). Chronically trained rainbow trout displayed an attenuation of the stress hormone cortisol in response to an acute bout of forced exercise compared with their untrained counterparts (Hernandez et al. 2002). Additionally, interval-trained Atlantic salmon displayed enhanced survival and attenuated cardiac pro-inflammatory cytokine response to a viral challenge (Castro et al. 2011). There is also evidence that the anxiolytic effect of exercise extends to fish. Mosquito fish exercise trained for 28 days by placement in a water tank with a constant current demonstrated behavioral changes consistent with an anxiolytic effect. Compared with untrained fish, trained fish displayed greater exploratory behavior in a novel context and had a reduced latency to leave a familiar refuge (Sinclair 2014). These data suggest that increasing physical activity status of the organism ubiquitously reduces consequences of stress across vertebrate taxa, although more work needs to be done to characterize the different species that can benefit from exercise.

One issue that arises when investigating the effects of exercise on brain and behavior is the ability to differentiate exercise effects from those of environmental enrichment. Including a wheel in a rat's cage, for example, provides an object on which the rat can climb and explore, and complex enriched housing environments engage cognitive processes and can initiate structural plasticity, enhance cognitive function, and increase stress resilience (Comery et al. 1995; Fan et al. 2007; Markham et al. 2009; Veena et al. 2009a, 2009b; Fischer 2015; Grimberg-Henrici et al. 2015; Hullinger et al. 2015; Ji et al. 2015; Novkovic et al. 2015). Many of the studies reporting beneficial effects of enriched environments, however, have included running wheels as part of the enriched housing. Recent work attempting to differentiate the effects of running from complex environmental enrichment have shown that at least some of the effects of long-term exercise in rodents are above and beyond those produced by environmental enrichment alone (Nyhuis et al. 2010; Kobilic et al. 2011; Mustroph et al. 2012). Thus, although cognitive engagement is certainly part of the exercise stimulus, and enriched environments that engage cognitive processes can certainly benefit brain plasticity and behavior, at least some of the effects of exercise are independent from these enrichment factors. An important goal of future studies should be to determine the role of cognitive engagement in the beneficial effects of exercise.

Potential Signals Responsible for Conveying the Effects of Exercise to Neural Circuits Involved in Cognitive Function and Stress

Data elucidating the intracellular signaling pathways, neurotransmitter systems, and means of synaptic plasticity that are sensitive to physical activity are rapidly emerging. However, a critical unanswered question is how the experience of exercise is communicated to the brain to result in altered neural activity, gene expression, or synaptic plasticity required for the observed behavioral effects of exercise. Indeed, the National Institutes of Health recently implemented a Common Fund with the goal of identifying these signals in exercising humans (<http://commonfund.nih.gov/MolecularTransducers>). We will refer to these potential means of exercise-to-brain communication simply as exercise signals. Exercise signals could originate from 2 sources: from the periphery or from within the central nervous system. Signals derived from the periphery could include activity of afferent nerves or

factors released from working muscle, among other factors (Figure 1). These signals would communicate with the brain in a “bottom-up” fashion, whereas central factors, such as psychological processes recruited during physical activity including learning exercise routines, choosing to exercise, exercise reward, or an increase in central arousal (Figure 1), would signal in a “top-down” manner. Exercise signals that could be involved in the effects of physical activity on adult neurogenesis in the hippocampus have been recently reviewed (Bolijn 2015). Some of these signals, as well as others that could be important for conferring the broad effects of physical activity on cognitive function and stress resistance, are shown in Figure 1.

Monoamines as Signaling Factors

Considering the array of behaviors and brain areas impacted by physical activity, and that many effects of physical activity seem to be conserved across the animal kingdom, it is possible that exercise signals derived from various sources could converge on a common target within the central nervous system that could then at least partly contribute to the wide variety of neural and behavioral changes elicited by exercise. Of these signals, monoamines such as dopamine (DA), NE, and 5-HT represent likely candidates. The current review focuses on NE and 5-HT because the majority of work focuses on these monoamines. Discussions on the potential role of DA can be found elsewhere (Knab & Lightfoot 2010; Greenwood et al. 2011; Monteiro-Junior et al. 2015). Consistent with a role for monoamines as exercise signals are the facts that monoamines: 1) are highly conserved, 2) innervate brain regions involved in cognitive function and stress from their metencephalic and mesencephalic origins, 3) have long been implicated in memory modulation and behavioral responses to stress, 4) are known to be sensitive to the physical activity status of the organism, and 5) respond to many of the exercise signals listed in Figure 1. The following sections will consider the involvement of NE and 5-HT in the behavioral effects of physical activity. Central to this theme is the idea that NE and 5-HT could represent key points of convergence between bottom-up and top-down signaling factors involved in communicating the experience of exercise to the brain circuits involved in cognitive processes and stress (Figure 1).

Role of NE in Cognitive Benefits of Exercise

Rodent models provide a convenient tool with which to study the mechanisms underlying the beneficial effects of exercise on behavior. Rodent studies investigating the effects of exercise on cognitive function have been hyperfocused on learning processes supported by the hippocampus. This attention to the hippocampus makes sense considering that hippocampus-dependent memory is readily assessed in rats and mice, and some of the most commonly observed effects of exercise are an increase in growth factors and birth of new neurons in the adult hippocampus. The hippocampus is thought to be important for learning and memory of contextual and spatial information (Rudy et al. 2002), as well as declarative memory. Interestingly, exercise-induced improvements in hippocampal function seem to be independent of exercise controllability: both forced treadmill training (Albeck et al. 2006; Griffin et al. 2009; Li et al. 2013; Inoue et al. 2015) or swimming (Chae et al. 2012), as well as voluntary access to running wheels (Merrill 1993; van Praag et al. 1999a; Vaynman et al. 2004; Greenwood et al. 2009), have been reported to enhance some types of memory. For this reason, exercise signals responsible for the effects of exercise on hippocampal function could be insensitive to the top-down signaling factor of exercise

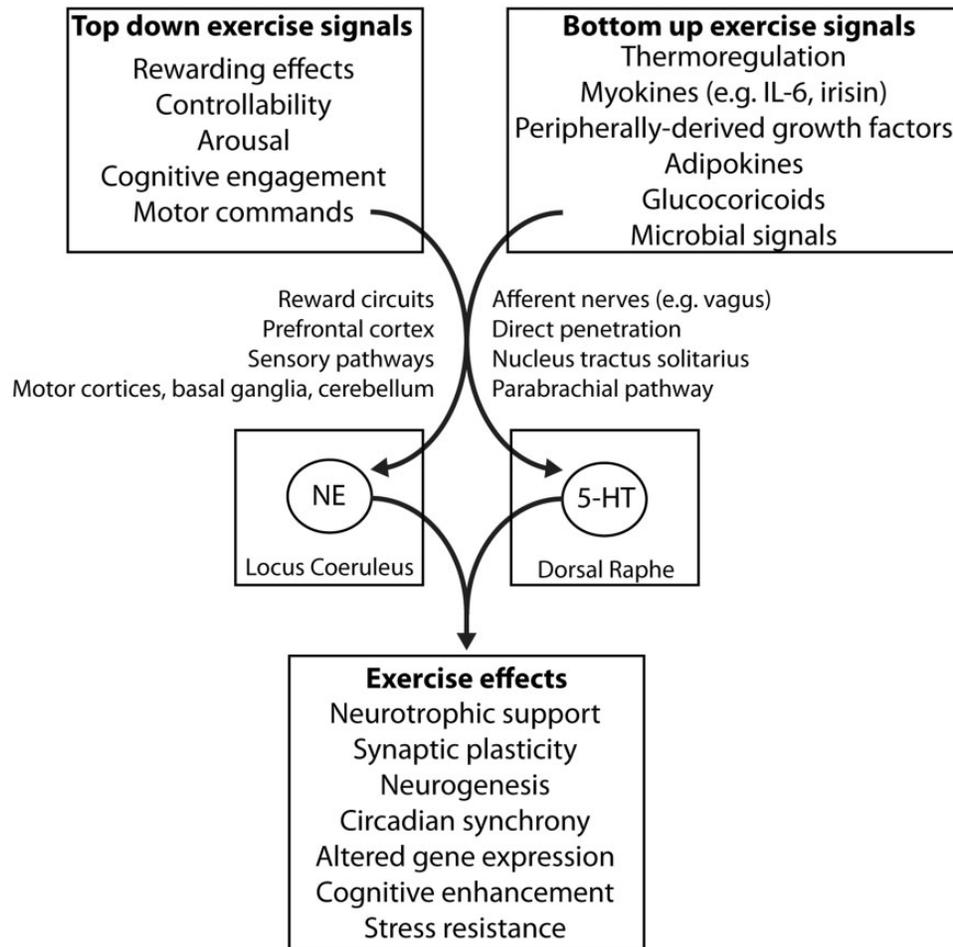


Figure 1. NE and 5-HT neurons of the locus coeruleus and dorsal raphe nucleus are a site of convergence of central (top-down) and peripheral (bottom-up) signals conveying the experience of exercise to brain circuits involved in cognition, stress, and emotional behavior.

controllability. Along with peripheral signaling factors released from muscle, central NE would likely be insensitive to the controllability of exercise, as NE neurons in the locus coeruleus (LC) are thought to be important for arousal, attention, and mood (Sara & Bouret 2012); states likely impacted by voluntary as well as forced exercise. This does not imply that all effects of exercise are insensitive to the type or controllability of exercise employed. Treadmill training, for example, fails to prevent stress-induced deficits in goal-directed learning thought to depend on the striatum (Greenwood et al. 2013).

Increases in neurogenesis and plasticity factors such as BDNF in the hippocampus are thought to be critical to the cognitive benefits of exercise (Cotman et al. 2007). Interestingly, similar to the benefits to hippocampal function, increases in BDNF and neurogenesis in the hippocampus are insensitive to exercise controllability. Both voluntary wheel running (Neeper et al. 1995; Oliff et al. 1998; Greenwood et al. 2009), forced wheel running (Leasure & Jones 2008), and forced treadmill training (Griffin et al. 2009; Kim et al. 2015) increase plasticity factors including BDNF in the hippocampus. Increases in circulating factors could be important for these hippocampal changes after exercise, and this possibility has been recently reviewed (Bolinj 2015). Often overlooked, however, is the contribution of NE to the hippocampal and cognitive effects of exercise (discussed previously in Greenwood & Fleshner 2013).

It is possible that the increase in plasticity factors could influence neural and behavioral effects of exercise by eliciting plastic changes in NE systems. BDNF, for example, has been shown to contribute to LC noradrenergic neuronal plasticity during development (Holm et al. 2003), aging (Matsunaga et al. 2006; Nakai et al. 2006), and in response to specific signals such as opioids that could be recruited during exercise (Akbarian et al. 2002). Repeated activation of NE systems during exercise could also directly influence plasticity factors. Prior work indicates that central NE systems (Dunn & Dishman 1991; Dunn 1996a; Dunn 1996b) including LC NE neurons (Greenwood & Fleshner 2013) are activated by exercise, and there are a variety of neuroplastic changes that occur in the NE system with chronic exercise that are consistent with repeated NE activation (Brown & Van Huss 1973; Ostman & Nyback 1976; Brown et al. 1979; Dishman 1997b; a; Dishman et al. 1997; Dishman et al. 2000). The LC receives input from autonomic regions of the medullary reticular formation and the nucleus of the solitary tract (NTS; Aston-Jones et al. 1991), as well as a recently identified dense projection from the cerebellum (Schwarz et al. 2015). These inputs suggest that the LC could be a site of integration between afferent information regarding medullary autonomic reflexes, including from the sensory vagus nerve relayed from the NTS, with motor information from the cerebellum. Thus, several bottom-up or top-down exercise signaling mechanisms could converge on LC NE activity, which would then

function to facilitate sensory gating, focus attention, or improve learning during exercise.

Of particular note is that activation of the LC via the vagus nerve could be a pathway through which circulating cytokines (Goehler et al. 2000; Guyon et al. 2008; Pedersen & Febbraio 2008) or products from optimized gut microbiota (Mika & Fleshner 2015; Mika et al. 2015b) signal the brain during exercise. Consistent with a role for gut microbiota are recent data reporting that wheel running can increase the abundance of beneficial microbial species in the rat gut, especially during early life (Mika & Fleshner 2015; Mika et al. 2015b). These microbes include *Lactobacillus* and *Anaerostipes* species that can release a variety of products including cytokines, neurotransmitters, and single chain fatty acids, which could communicate with the brain through vagal afferent signaling. Central 5-HT systems could be an additional central target of vagal nerve-mediated NE activity through a mechanism involving $\alpha 1b$ -adrenergic receptor (ADR) located on raphe 5-HT neurons (Day et al. 2004). Indeed, repeated stimulation of the vagus nerve activates 5-HT neurons in the dorsal raphe nucleus (DRN; Manta et al. 2009) and elicits increases in extracellular levels of both NE and 5-HT in the hippocampus and cortex (Manta et al. 2013).

Increases in NE release could influence learning and cognitive function by initiating plasticity in target regions of the LC. For example, β -ADRs are linked to the transcription of BDNF through adenosine 3', 5'-monophosphate (cAMP)-dependent protein kinase (PKA)-induced phosphorylation of cAMP response element-binding protein (CREB; (Conti et al. 2002)). Most importantly, the increase in hippocampal BDNF after exercise has been shown to be dependent on central noradrenergic signaling. Blockade of either CREB (Chen & Russo-Neustadt 2009) or β -ADRs (Ivy et al. 2003) prevents the exercise-induced increase in BDNF and the improved contextual memory typically observed after 6 weeks of wheel running (Van Hooymissen et al. 2004). Additionally, Garcia et al. (2003) reported that N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (DSP-4) lesions of the LC reduces BDNF mRNA in the hippocampus of exercised rats to a level equivalent to sedentary rats, which are unaffected by DSP-4 lesions (Garcia et al. 2003). This potential role of NE in exercise-induced plasticity and cognitive enhancement is similar to the suggested contribution of noradrenergic signaling to the increase in BDNF after administration of chronic antidepressants (Duman & Monteggia 2006).

NE could contribute to other benefits of exercise in addition to initiating neural plasticity in the hippocampus. LC NE neurons also project to the prefrontal cortex and amygdala. NE in these regions could contribute to modulation of attention and executive function (Berridge & Spencer 2015), as well as emotional behavior. For example, acute wheel running in close proximity to the acquisition phase of fear extinction enhances fear extinction memory (Siette et al. 2014) and reduces the relapse of conditioned fear responding after extinction (Mika et al. 2015a). NE has similar effects. Infusion of the mixed β -ADR agonist isoproterenol directly into the medial prefrontal cortex (PFC), including the infralimbic region, immediately before acquisition of contextual fear extinction enhances the learning and retention of contextual fear extinction (Do-Monte et al. 2010). Microinfusions of NE into the basolateral amygdala immediately after extinction of contextual fear enhance the consolidation of fear extinction memory (Berlau & McGaugh 2006). Given that exercise activates LC NE neurons, these data suggest that NE could contribute to the facilitation of fear extinction produced by acute exercise. However, it is unlikely that NE is solely responsible, as NE agonists seem to only enhance the recall of fear extinction memory if memory testing occurs in the context in which fear extinction learning

occurred (Morris & Bouton 2007). In contrast, exercise during the acquisition of fear extinction prevents the relapse of fear in novel contexts (Mika et al. 2015a). Nevertheless, LC NE systems could contribute to a variety of neuroplastic, cognitive, and emotional effects of exercise. Related to this idea are data demonstrating that galanin, a neuropeptide co-expressed with NE in LC neurons, contributes to anxiolytic and stress-protective effects of exercise (Sciolino & Holmes 2012; Sciolino et al. 2015).

Central 5-HT Systems and Exercise-Induced Stress Resistance

In addition to NE, 5-HT has been implicated in contributing to the beneficial effects of exercise on brain function and behavior. Research has focused on changes in central 5-HT systems after exercise, and how these changes could contribute to antidepressant, anxiolytic, and stress-buffering effects of exercise (reviewed in Dishman 1997a; Greenwood & Fleshner 2011). The 5-HT system displays alterations in gene expression and functional activity after an increase in physical activity in animals as diverse as humans and lizards. The changes in 5-HT systems after exercise include adaptations both within cell body regions in raphe nuclei (Greenwood et al. 2003a, 2005b; Loughridge et al. 2013) as well as adaptations in raphe target regions involved in regulating specific behaviors (Chaouloff 1994; Dishman et al. 1997; Greenwood et al. 2012; Christianson & Greenwood 2014). It should be mentioned that prior work investigating the effects of forced exercise such as treadmill training on central 5-HT systems should be interpreted with caution. Specific 5-HT systems are quite sensitive to stress (described below), and treadmill training can be a potent stressor (Brown et al. 2007) that produces inconsistent results in animal models of stress-related disorders (Burghardt et al. 2004; Greenwood et al. 2013; Hong et al. 2015; Kim et al. 2015). There is recent evidence that the stressor intensity of the treadmill training protocol could contribute to the divergent effects of treadmill training on stress-resistance and emotional behavior. Otsuka et al. (2015) ran rats on a treadmill for 30 min at varying intensities. Only low-intensity training reduced anxiety- and depression-like behavior in the elevated plus maze and forced swim test, respectively. High-intensity treadmill running activated the HPA axis as indicated by *cFos* expression in corticotropin releasing factor-containing neurons in the hypothalamus, and did not alter behavior (Otsuka et al. 2015). Another recent study reported that although both high and low intensity forced treadmill training increased dentate gyrus volume and cell proliferation, high-intensity exercise increased circulating corticosterone, whereas only low-intensity treadmill training increased the survival of the newly born neurons (Inoue et al. 2015).

In the remainder of the current review, we briefly summarize prior work on the effects of exercise on 5-HT systems, add discussion of new data, and consider the signals by which exercise could communicate with central 5-HT systems. In particular, we discuss data suggesting that thermoregulation could be an important factor signaling the experience of exercise to the central 5-HT system.

Populations of 5-HT Neurons Differ in Their Roles in Stress and Emotional Behavior

The majority of 5-HT innervating the forebrain in vertebrates originate in the midbrain DRN. The role of DRN 5-HT neurons in behavioral responses to stress and emotional behavior has been extensively

investigated (Graeff et al. 1996; Clark & Neumaier 2001; Lowry et al. 2005; Maier & Watkins 2005; Richardson-Jones et al. 2010; Paul & Lowry 2013; Paul et al. 2014). One theme that emerges from this work is that 5-HT neurons in the DRN are heterogeneous in terms of receptor expression, projection sites, and roles in emotional behavior (Figure 2). For example, subsets of DRN 5-HT neurons located in the rodent dorsal and ventral aspects of the mid-DRN, and in the dorsal aspect of the caudal DRN, seem to contribute to the development of anxiety and depression after stress (Lowry et al. 2008). Within this stress-promoting region of the DRN are 5-HT neurons projecting to the basolateral amygdala and dorsal striatum (Commons et al. 2003; Hale et al. 2008, 2012), structures critical for processing fear- and anxiety-related stimuli (LeDoux 2003) and goal-directed learning (Yin et al. 2005), respectively; and in which 5-HT can elicit anxiety and deficits in goal-directed learning through a mechanism involving 5-HT_{2C}R (Christianson et al. 2010; Strong et al. 2011; Greenwood et al. 2012; Christianson & Greenwood 2014). Consistent with a role for subsets of DRN 5-HT neurons promoting stress and anxiety are the observations that exposure to diverse anxiety-eliciting drugs (Abrams et al. 2005; Lawther et al. 2015), social defeat (Gardner et al. 2005), an anxiogenic open-field (Hale et al. 2008), or uncontrollable stress (Grahn 1999; Greenwood et al. 2003a), all potently and selectively activate 5-HT neurons in these stress-promoting DRN subregions. Moreover, controllable stress, which does not produce anxiety and in fact leads to protection against future uncontrollable stressors, inhibits activity of these stress-promoting DRN 5-HT subsets (Amat et al. 2005, 2010).

In contrast to the stress-promoting DRN 5-HT neurons, 5-HT neurons located in the ventrolateral and interfascicular regions of the DRN are implicated in inhibition of panic, enhanced stress coping, and anxiolytic responses (Figure 2; Hale et al. 2012, 2013; Paul & Lowry 2013; Paul et al. 2014). These 5-HT neurons project heavily to the hippocampus, medial septum, and regions of the prefrontal cortex thought to be dysregulated in depressed subjects (Drevets 2000). The idea that distinct 5-HT systems modulate

affective state, whereby one promotes anxiety and depression and the other stress coping, allows the possibility that disruption in either system (i.e., hyperactivity of the stress-promoting region or hypoactivity of the stress-protective region) could lead to stress-related disorders. Indeed, this dual role of 5-HT in emotional behavior could explain discrepancies in the literature regarding the role of 5-HT in depression.

Exercise Shifts Activity of Stress-Responsive 5-HT Systems from Stress-Promoting to Stress-Protective

Given the potential dual role of DRN 5-HT neurons in emotional and stress-related behaviors, it is possible that exercise could promote stress resistance by either attenuating activity of stress-promoting 5-HT systems and/or increasing activation of stress-protective 5-HT systems. There is evidence that exercise does both. Six weeks of voluntary wheel running attenuates the number of DRN 5-HT neurons expressing the neural activity marker c-Fos after acute exposure to an uncontrollable stressor (Greenwood et al. 2003a). The most robust effect of exercise was observed in the dorsal and ventral regions of the rostral—mid DRN; those same regions implicated in promoting anxiety and deleterious behavioral effects of stress. Exposure to the same acute stressor potentiates 5-HT efflux in the dorsal striatum in response to subsequent exposure to mild stress, which can interfere with goal-directed learning through a mechanism involving 5-HT_{2C}R (Strong et al. 2011). Six weeks of voluntary wheel running also prevented the stress-induced exaggerated 5-HT efflux in the dorsal striatum (Clark et al. 2015) and the corresponding deficits in goal-directed escape learning (Greenwood et al. 2003a).

Interestingly, constraint over activation of stress-responsive 5-HT systems after exercise was also observed in male *Anolis carolinensis* lizards. Acute restraint stress increased the 5HIAA/5-HT ratio in the striatum and nucleus accumbens, indicative of high 5-HT activity in

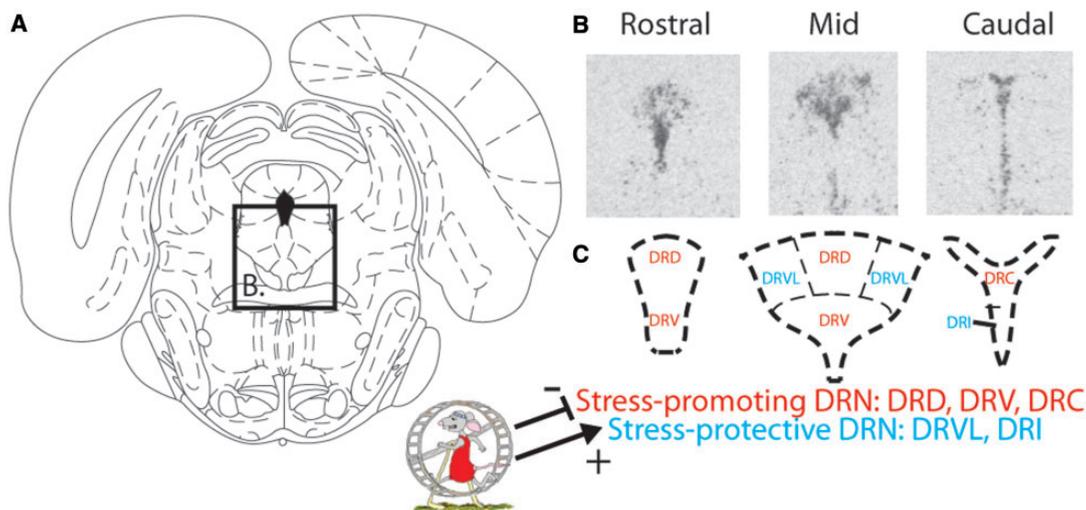


Figure 2. Dual role of DRN serotonergic (5-HT) neurons in stress and emotional behavior. (A) Cartoon of the rat midbrain modified from the Rat Brain Atlas in Stereotaxic Coordinates (Paxinos, 1998) with the location of the DRN highlighted. (B) Coronal sections of the rat DRN showing expression of tryptophan hydroxylase 2 mRNA labeled with in situ hybridization at rostral, mid, and caudal DRN levels. (C) Cartoon depicting a simplified version of subpopulations of DRN 5-HT neurons involved, in general, in the promotion of stress and anxiety behaviors (stress-promoting DRN 5-HT neurons; red), or in stress coping and anxiolytic effects (stress-protective DRN 5-HT neurons; blue). Exercise constrains activation of stress-promoting DRN 5-HT neurons and activates stress-protective DRN 5-HT neurons. DRD, dorsal aspect of the DRN; DRV, ventral aspect of the DRN; DRVL, ventrolateral aspect of the DRN; DRC, caudal aspect of the DRN; DRI, interfascicular region of the DRN.

these regions. Acute exercise reversed this stress-induced 5-HT activity (Emerson et al. 2000). It makes sense that constraint over activity of striatum-projecting 5-HT neurons would be a conserved exercise adaptation. Serotonin in discrete brain regions including the striatum is thought to contribute to the initiation of central fatigue during exercise (Bailey et al. 1992; 1993b; Davis & Bailey 1997), perhaps by reducing DA efflux required to maintain motor activity (De Deurwaerdere et al. 2004). Thus, in addition to protection against deleterious emotional effects of stress, the development of constraint over activation of stress- and fatigue-promoting DRN 5-HT systems after chronic exercise could serve to delay the onset of fatigue during intense exercise bouts, a common training effect.

Exercise not only results in dynamic changes in serotonergic responses to stress, it also produces static changes in gene expression within cell body regions and terminal sites of central 5-HT circuits. Indeed, a microarray analysis indicated that voluntary wheel running dramatically alters gene expression within laser-captured neurons of the stress- and anxiety-promoting region of the DRN (Loughridge et al. 2013). One of the DRN genes that increases in expression after exercise is the gene coding for the 5-HT_{1A} inhibitory autoreceptor (Loughridge et al. 2013). Notably, the increase in 5-HT_{1A} mRNA occurs in the same region of the DRN showing the biggest attenuation in activity after stressor exposure in physically active rats (Greenwood et al. 2003a, 2005b), and in a time course consistent with the protective effect of exercise against stress-induced anxiety- and depression-like behaviors (Greenwood et al. 2005a). Because 5-HT_{1A} mRNA is almost exclusively co-localized with 5-HT transporter mRNA in the DRN (Day et al. 2004), and wheel running attenuates activity of DRN 5-HT neurons in the stress-promoting DRN, it is a reasonable assumption that the difference in 5-HT_{1A} mRNA in the DRN produced by exercise results in a functional increase in 5-HT_{1A} autoreceptors. An increase in 5-HT_{1A}-mediated autoinhibition is one mechanism by which exercise could lead to constraint over activity of stress-promoting DRN 5-HT neurons during exposure to stress.

Exercise also alters expression of 5-HT-related genes in terminal regions of the DRN. For example, 6 weeks of voluntary wheel running reduces 5-HT_{2C}R mRNA in the dorsal striatum and amygdala (Greenwood et al. 2012). Adaptation in these regions could be particularly important for effects of exercise on emotional behavior. Thus, exercise seems to produce protection against the stress-promoting effects of 5-HT at multiple levels: one being within the DRN through constraint of neural activity, and another being resistance to the effects of 5-HT through downregulation of post-synaptic receptors. Consistent with this idea are the observations that wheel running produces resistance to the depression- and anxiety-like behaviors elicited by microinjection of a 5-HT_{2C}R agonist directly into the dorsal striatum or amygdala (Greenwood et al. 2012), as well as by rapid increases in extracellular 5-HT elicited by acute systemic administration of a selective 5-HT reuptake-inhibitor (Greenwood et al. 2008).

Constraint over stress-induced 5-HT signaling, particularly at 5-HT₂ receptors, could not only be an important contributor to the stress-buffering effects of exercise on emotional behavior, but could also contribute to memory-boosting effects of exercise in the face of stress. In addition to interfering with goal-directed learning through a serotonergic mechanism in the striatum (Strong et al. 2011), stress can damage hippocampal circuits leading to memory impairments (McEwen et al. 2015). Although whether beneficial effects of exercise extend to protection against stress-induced memory impairments is still an active area of inquiry, several observations suggest that it would. First, exercise can prevent the hippocampal-dependent memory impairments and amnesia produced by acute or chronic

stress (Fleshner et al. 2014; Patki et al. 2014). Second, exercise prevents reductions in hippocampal BDNF mRNA and protein produced by exposure to a severe acute stressor (Adlard & Cotman 2004; Greenwood et al. 2007). Unlike the effect of NE on BDNF which is stimulatory, the effects of 5-HT on BDNF are mixed. Consistent with divergent behavioral effects of different subpopulations of 5-HT neurons is the observation that 5-HT seems to have opposing effects on BDNF mRNA in different brain regions. For example, although 5-HT increases BDNF in the cortex (Vaidya et al. 1997), activation of 5-HT₂ receptors in the hippocampus is necessary (Vaidya et al. 1999) and sufficient (Vaidya et al. 1997; Fleshner et al. 2014) for stress-induced reductions in BDNF. Therefore, constraint over 5-HT neural activity could help preserve hippocampal-dependent memory even in the face of stress. Together, these data suggest that constraint over stress-promoting DRN 5-HT systems is a conserved effect of exercise that could contribute to resistance against both stress-induced anxiety- and depression-like behavior, as well as impaired cognitive function.

Exercise not only attenuates activity of stress and anxiety-promoting 5-HT systems, it also activates anxiolytic 5-HT systems. Recording from DRN 5-HT neurons during physical activity in cats and rats, Jacobs and Fornal demonstrated that 5-HT neuronal activity is acutely responsive to exercise (Jacobs & Fornal 1993; 1997; 1999). These data led Jacobs and Fornal to hypothesize that midbrain 5-HT neurons play a pivotal role in the control of movement. A plethora of additional data, including 1 report in Anolis carolinensis lizards (Emerson et al. 2000), are consistent with 5-HT responding to acute exercise (Chaouloff 1989; Chaouloff et al. 1989; Dey et al. 1992; Bailey et al. 1993a). The majority of this prior work, however, utilized forced running on a treadmill. Data suggesting increases in 5-HT activity after voluntary exercise are limited (Dishman 1997a). Voluntary wheel running elicits the biggest changes in gene expression in the rostral DRN (Greenwood et al. 2005b), the region of the DRN most intimately connected with the motor region of the basal ganglia (Steinbusch et al. 1981). Interestingly, axons of some 5-HT neurons in the rostral DRN have been reported to branch and project to both the basal ganglia and the amygdala (Imai et al. 1986); thus, providing a potential site of interplay between motor activity and emotional behavior within the 5-HT system. Although there is limited evidence that repeated activity of the 5-HT system during exercise is necessary for the stress-protective effects of exercise, one study reported that depleting 5-HT with PCPA prevented the antidepressant-like effects of voluntary wheel running in the forced swim and tail suspension tests, 2 rodent models of depression-like behavior (Cunha et al. 2012). Together, these data suggest that exercise recruits 5-HT systems, but whether exercise-induced activation is independent of an aversive stress response and is selective to stress-protective populations of DRN 5-HT neurons remains to be determined.

Potential Signals Communicating the Effects of Exercise to the 5-HT System

It is not clear what signals drive the changes in the central 5-HT system after exercise, but several top-down and bottom-up signaling possibilities are provided in Figure 1. One possibility is that repeatedly choosing to exercise and exerting control over that exercise elicits plasticity in prefrontal-cortical-striatal circuits capable of inhibiting stress-promoting DRN 5-HT neurons during stress (Maier et al. 2006; Maier 2015). However, the observation that the protective

effect of exercise occurs in rats with lesions of the prefrontal cortex does not support this mechanism (Greenwood et al. 2013; Christianson & Greenwood 2014). An additional scenario is communication between brain reward circuits and the serotonergic system. Indeed, both voluntary (Lett et al. 2000; Greenwood et al. 2011) and forced (Herrera et al. forthcoming) wheel running are rewarding and activate central reward circuitry. Neurons in the nucleus accumbens responding to rewarding stimuli could communicate with DRN 5-HT neurons either through direct projections (Zhang et al. 2013) or indirectly through the habenula (Hong & Hikosaka 2008). In addition to these top-down exercise signals, 5-HT neurons could simply respond to incoming motor-related sensory information and, as such, be a primary player in driving motor activity, as hypothesized by Jacobs and Fornal (1993). Repeated top-down recruitment of 5-HT systems during exercise could then lead to plastic changes within stress-promoting DRN 5-HT systems, which could contribute to the constraint over their activity during stressor exposure. Future studies are required to test this hypothesis.

In addition to responding to top-down exercise signals, DRN 5-HT neurons could be signaled by peripheral, bottom-up factors such as the vagus nerve, as well as growth factors. Similar to the sensitivity of LC NE neurons to growth factors, BDNF receptor TrkB is expressed on DRN 5-HT neurons (Madhav et al. 2001), and intra-DRN administration of BDNF altered firing patterns of DRN 5-HT neurons (Celada et al. 1996). It is also possible that input from the LC drives the changes in gene expression observed in the stress-promoting 5-HT system in response to exercise. Noradrenergic projections from the LC to the DRN target the rostral portion of the DRN most heavily (Peyron et al. 1996), and it is the rostral region of the DRN that shows the greatest response to wheel running (Greenwood et al. 2005b).

An additional bottom-up signaling factor not previously discussed is thermoregulation during exercise. Serotonergic neurons are part of the central circuitry underlying thermoregulatory cooling (Lowry et al. 2009; Madden & Morrison 2010). Increases in ambient heat, core, and skin temperature activate DRN 5-HT neurons via the spinal–parabrachial pathway (Hale et al. 2011). Notably, whereas stress-promoting populations of DRN 5-HT neurons respond minimally to warm temperature; the stress-protective regions of the DRN include the temperature-sensitive 5-HT neuron population (Hale et al. 2011, 2013). Activation of the stress-protective DRN by increases in body temperature is consistent with emerging data suggesting that increasing temperature is indeed anxiolytic and antidepressant (reviewed in Raison et al. 2014). A small clinical trial in adults diagnosed with major depressive disorder, for example, demonstrated that whole-body hyperthermia can reduce depression symptoms (Hanusch et al. 2013). Moreover, human functional magnetic resonance imagery studies reveal that feelings of pleasantness elicited by warm (41 °C) cutaneous stimuli activates the mid-orbitofrontal cortex, pregenual cingulate cortex, and the ventral striatum (Rolls et al. 2008); areas that are dysregulated in depression (Drevets et al. 2008) and that receive 5-HT projections from the stress-protective DRN (Van Bockstaele et al. 1993). These data support the hypothesis proposed by Lowry & colleagues that function of the temperature-sensitive, stress-protective DRN is impaired in depressed patients, and successful antidepressant strategies restore function in this area (Lowry et al. 2009; Hale et al. 2013; Raison et al. 2014). Consistent with this idea are the observations that depressed patients have impaired thermoregulatory cooling (Ward & Doerr 1986), and a common “side effect” of antidepressant drugs is an increase in sweating (i.e., thermoregulatory cooling; Marcy & Britton 2005). These data allow the hypothesis that, similar to the acute antidepressant effect of

increases in temperature, the transient increase in temperature and thermoregulatory cooling during exercise could be responsible for the mood-enhancing effects of exercise by activating the temperature-sensitive, stress-protective DRN. Indeed, data indicate that the temperature-sensitive DRN 5-HT neurons are responsive to exercise. In a preliminary study, rats with a history of 6 weeks of access to running wheels were sacrificed during the peak of their active cycle and immunohistochemistry was used to measure the effect of acute exercise on immediate early genes. Compared with rats housed with locked wheels, chronic runners responded with an increase in FosB/ΔFosB in 5-HT neurons of the interfascicular DRN (Arnold 2015), one of the regions responding most robustly to increases in temperature (Hale et al. 2011; Hale et al. 2013). In summary, it is possible that either top-down or bottom-up exercise signals including thermoregulation could lead to the changes in gene expression observed in the central 5-HT system after exercise, constraint over 5-HT neural activity, and stress resistance.

Summary

Physical activity enhances cognitive function and improves stress resistance and mental health. A variety of plastic changes contribute to the effects of exercise, including structural changes within brain circuits, enhanced neurotrophic support, neurogenesis, and modulation of gene expression. Many of the effects of exercise on brain and behavior are observed in a variety of species; suggesting ubiquitous exercise signaling mechanisms that are conserved among vertebrates. Longstanding and recent data are consistent with the idea that the conserved monoamines NE and 5-HT could mediate the effects of exercise on brain circuits involved in cognition and stress. NE and 5-HT systems are sensitive to both peripheral signals and central neural circuits recruited during exercise; thus, they represent important nodes of convergence between top-down and bottom-up exercise signals. Exercise signals potentially targeting central monoaminergic systems include those originating from the periphery, such as microbial products, myokines, adipokines, growth factors, glucocorticoids, and temperature; as well as those originating from within-brain circuits recruited during exercise such as primary motor regions (cortex, basal ganglia, cerebellum), prefrontal–striatal controllability circuits, reticular activating system–arousal centers, reward circuits, and sensory-motor circuits involved in the cognitive engagement occurring during exercise.

Considering the array of signals capable of recruiting NE and 5-HT systems during exercise, it is unlikely that any one of these signals is going to be solely necessary for the beneficial impact of exercise on brain function and behavior. However, it is possible that signals differ in their importance for mediating specific exercise effects. Information regarding which type, duration, and intensity of exercise optimally recruit specific exercise signals could therefore be potentially useful to tailor exercise programs to specific benefits. Finally, one of the primary uses of exercise neuroscience research could be as a tool to identify novel signals and targets that, although most likely not solely necessary for exercise effects, could be sufficient to act independently of exercise as cognitive enhancers or stress prophylactic strategies.

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