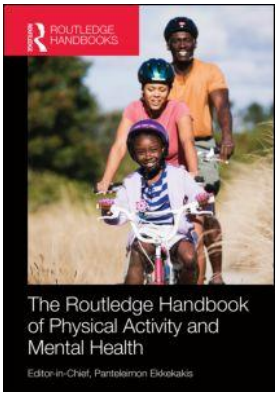

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Mechanisms Underlying the Relationship Between Physical Activity and Anxiety

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MECHANISMS UNDERLYING THE RELATIONSHIP BETWEEN PHYSICAL ACTIVITY AND ANXIETY

Animal data

Benjamin N. Greenwood and Monika Fleshner

It is well established that physical activity can reduce the incidence and severity of anxiety disorders (see Chapter 5 by Utschig et al., this volume). Despite the anxiolytic effects of physical activity in humans, the underlying mechanisms remain unknown. Identification of these mechanisms could enhance our understanding of anxiety and lead to more effective therapeutic or preventative strategies.

The limited understanding of the mechanisms underlying the anxiolytic effects of exercise could be due, in part, to the mixed results of animal studies on the effects of exercise on anxiety. Indeed, the effects of exercise in rodent models of anxiety is far from clear, with both anxiolytic and anxiogenic effects being reported. Despite the confusion, progress has been made toward understanding the mechanisms by which physical activity prevents anxiety. In the current chapter, we attempt to interpret the data on the behavioral effects of exercise on animal models of anxiety. We will offer a perspective on the available data that suggest specific experimental conditions under which anxiolytic effects of exercise are maximally revealed. The hope is that understanding the sometimes subtle behavioral impact of exercise in animal models will help uncover the neurobiological mechanisms underlying the effects of exercise on anxiety states. To this end, potential mechanisms will be discussed in the context of the behavioral effects of exercise on various rodent models of anxiety, including tests of learned anxiety, unlearned anxiety, and stress-induced anxiety.

Learned anxiety

Models of learned anxiety are based on assessing conditioned responses to stimuli previously associated with aversive events. During a typical rodent fear conditioning paradigm, a neutral, conditioned stimulus (e.g., a context or a tone) is paired with an aversive stimulus (such as a shock), so that subsequent exposure to the context or tone elicits a fear response in the absence of the aversive stimulus. The fear response in these experiments is most readily assessed using freezing or potentiation of the acoustic startle reflex. Freezing, the absence of all movement

except that required for respiration, is a species-typical defensive reaction that is elicited by exposure to a conditioned stimulus. An exaggerated conditioned fear response (be it freezing or startle) to the conditioned stimulus or a fear response elicited by a stimulus that only vaguely resembles the conditioned stimulus (i.e., fear generalization) are thought to be inappropriate fear responses and thus representative of anxiety (Maier & Watkins, 1998).

Behavioral effects of exercise on animal models of learned anxiety

The majority of the literature suggests that exercise facilitates contextual fear conditioning. When a rat with a history of prior wheel running is conditioned to fear a context, the exercised rat displays more freezing behavior than his sedentary counterpart when re-exposed to the conditioned context. This basic observation has been replicated by numerous investigators in both male and female rats and mice. The effects of exercise on fear conditioning are difficult to interpret in terms of anxiety. The increase in conditioned freezing elicited by exercise can be viewed as an inappropriate fear response (i.e., anxiety) or as a consequence of enhanced memory processes that cannot be distinguished from anxiety during a simple fear conditioning test.

Several experimental observations support the second interpretation. First, the effect of exercise on conditioned fear is relatively specific to freezing elicited during re-exposure to a conditioned context and is not generalized to all forms of conditioning. For example, exercise has no effect on freezing immediately following shock (Baruch, Swain, & Helmstetter, 2004; Burghardt, Pasumarthi, Wilson, & Fadel, 2006; Greenwood, Foley, Burhans, Maier, & Fleshner, 2005; Greenwood et al., 2003; J. D. Van Hoomissen, Holmes, Zellner, Poudevigne, & Dishman, 2004) or to a tone previously paired with shock (Baruch et al., 2004; Hopkins & Bucci, 2010); however, see Falls, Fox, & MacAulay, 2010. These data support the idea that exercise enhances function of a mechanism supporting contextual memory rather than one supporting fear, per se. The hippocampus normally supports context memory (Rudy, Barrientos, & O'Reilly, 2002), whereas other structures such as the amygdala can support freezing immediately following shock (Kim, Rison, & Fanselow, 1993) and CS-US associations (Huff & Rudy, 2004; Phillips & LeDoux, 1992). Consistent with exercise enhancement of contextually conditioned fear being a consequence of improved hippocampal-dependent learning and memory and not blatant anxiety, are the observations that both wheel running and treadmill training improve learning in other hippocampus-dependent tasks including the Morris water maze and object recognition (e.g., Clark et al., 2008; Garcia-Capdevila, Portell-Cortes, Torras-Garcia, Coll-Andreu, & Costa-Miserachs, 2009; Grace, Hescham, Kellaway, Bugarith, & Russell, 2009; Vaynman, Ying, & Gomez-Pinilla, 2004). Finally, if the increase in conditioned fear produced by exercise represents anxiety, we might expect to observe other signs of anxiety such as generalization of fear to environments different from the conditioned context. Indeed, over-consolidation of fear memories has been suggested to underlie symptoms of anxiety, such as phobias, intrusive thoughts, nightmares, and generalization of fear (Elzinga & Bremner, 2002). Instead, quite the opposite is observed in physically active rats. When a sedentary rat previously conditioned to fear one context is exposed to a different context sharing only limited features with the original context, it displays a small amount of freezing, which is representative of generalization of fear from the conditioned context to the new one. A rat previously allowed voluntary access to a running wheel, on the other hand, displays similar (J. Van Hoomissen et al., 2011) or less (Greenwood, Strong, Foley, & Fleshner, 2009) freezing in the new context compared to a sedentary rat, despite freezing more when placed back into the original conditioned context. These data suggest that exercise specifically improves the memory of the conditioned context, as well as the ability of the hippocampus to discriminate between contexts (Mizumori, Smith, & Puryear, 2007).

Based on these data, we offer the following interpretation of the effects of exercise on learned anxiety. Exercise does not enhance fear per se, but improves memory of the conditioned context. Improved memory of the conditioned context could be adaptive as the organism is more likely to avoid that environment in the future. Fear is particularly inappropriate when it is expressed in environments that were not previously paired with an aversive stimulus (i.e., generalization). Excessive generalization of fear could lead to avoidance of novel environments or experiences that might otherwise be safe. Here is where the anxiolytic effect of exercise can be observed. Enhanced ability to discriminate safe from dangerous contexts could aid physically active organisms from displaying excessive fear responses during relatively innocuous situations, such as exposure to environmental novelty. Consistent with this idea, exercise also attenuates the hypothalamic–pituitary–adrenal axis response to exposure to a novel environment (Campeau et al., 2010; Dishman et al., 1998). One implication of this interpretation is that the anxiolytic effects of exercise in models of learned anxiety are subtle and can only be revealed using experiments designed specifically to uncover them, such as tests of context discrimination.

Potential mechanisms

Although the mechanism by which exercise facilitates context discrimination is unknown, the facilitation of context discrimination could be a direct consequence of the enhanced memory of the conditioned context. Indeed, generalization can be inversely related to the strength of the original contextual memory, such as occurs as memories age (Wiltgen & Silva, 2007). Understanding how exercise enhances context memory could, therefore, provide insight into the mechanisms by which exercise improves context discrimination and reduces anxiety.

Potential mechanisms underlying the anxiolytic effect of exercise in models of learned anxiety are depicted in Figure 7.1. Because the effects of exercise on fear conditioning seem to be relatively selective to behaviors dependent upon hippocampus-dependent memory, and specifically the consolidation phase of memory (Falls et al., 2010; Greenwood et al., 2009), exercise-induced neuroplasticity in the hippocampus could contribute to the anxiolytic effect of exercise. Exercise increases the birth and survival of new neurons in the adult hippocampus (van Praag, Kempermann, & Gage, 1999), a process that could be important for some behavioral effects of antidepressant drugs (Santarelli et al., 2003). Clark et al. (2008), however, reported that the enhancement of contextual memory produced by wheel running in mice is independent of adult hippocampal neurogenesis (Clark et al., 2008). Although neurogenesis could remain important for the improvement in context discrimination provided by exercise, data are consistent with important roles for other factors relating to memory consolidation, such as neurotrophic factors and other regulators of synaptic plasticity.

Brain-derived neurotrophic factor (BDNF) is a neurotrophic factor implicated in hippocampus-dependent learning and memory and the consolidation phase of contextual fear conditioning (Poo, 2001; Tyler, Alonso, Bramham, & Pozzo-Miller, 2002). Genetic increases in BDNF can improve spatial learning and memory (Yukako et al., 2008), and neutralization of BDNF with intrahippocampal injection of a BDNF antibody eliminates the beneficial effects of exercise on hippocampus-dependent memory tasks (Ding, Ying, & Gomez-Pinilla, 2011; Vaynman et al., 2004). BDNF, therefore, could be an important player in the mechanisms underlying exercise-facilitation of memory consolidation and context discrimination. Voluntary wheel running increases BDNF mRNA and protein in the hippocampus (Berchtold, Chinn, Chou, Kesslak, & Cotman, 2005; Greenwood, Strong, Foley, Thompson, & Fleshner, 2007; Neeper, Gomez-Pinilla,

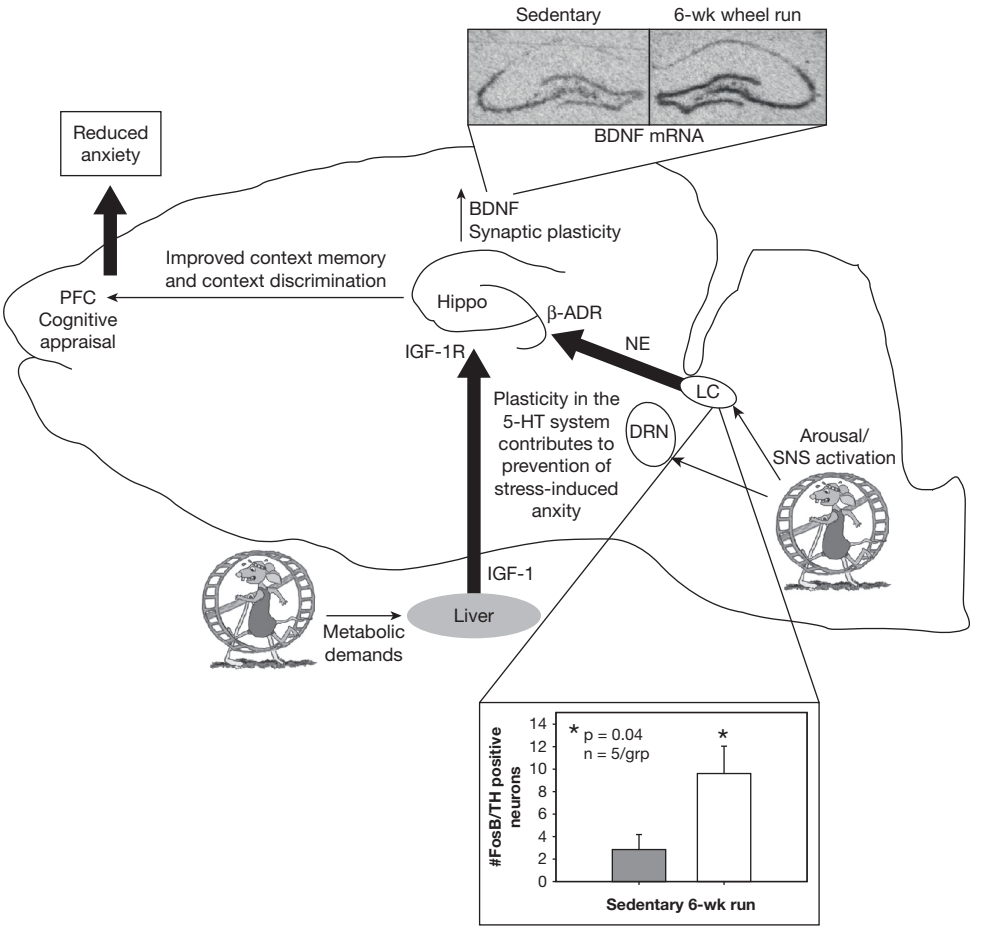

Figure 7.1 Potential mechanisms underlying the anxiolytic effects of exercise in animal models of learned anxiety. β-ADR, β-adrenergic receptor; BDNF, brain-derived neurotrophic factor; DRN, dorsal raphe nucleus; IGF-1, insulin-like growth factor-1; IGF-1R, insulin-like growth factor-1 receptor; LC, locus coeruleus; NE, norepinephrine; PFC, prefrontal cortex; TH, tyrosine hydroxylase.

Choi, & Cotman, 1995), including the ventral portion of the hippocampus (Greenwood et al., 2009), which has been particularly implicated in emotion regulation. For in-depth discussions on the potential role of BDNF in the beneficial effects of exercise, see Cotman, Berchtold, & Christie, 2007; Ding et al., 2011; Russo-Neustadt & Chen, 2005.

An interesting topic of inquiry is identification of the signal by which the experience of exercise is communicated to the brain resulting in alterations in anxiety or other behavioral effects of exercise. Such a signal could be peripherally or centrally derived. One potential peripherally derived signal is insulin-like growth factor-1 (IGF-1). Centrally derived signals could include the catecholamine neurotransmitter norepinephrine (NE). Both IGF-1 (Scofield et al., 2011), as a result of metabolic demands and growth hormone signaling to liver, and central NE (Kitaoka et al., 2010; Meeusen et al., 1997), as a result of increased arousal and sympathetic nervous system

activation, can be elevated following exercise. Peripheral IGF-1 begets central IGF-1 (Ding, Vaynman, Akhavan, Ying, & Gomez-Pinilla, 2006; Yan et al., 2011), where IGF-1 acts as a neurotrophin similar to BDNF. Reducing central IGF-1 prevents the exercise-induced increase in BDNF while leaving BDNF levels in sedentary rats intact (Ding et al., 2006). Moreover, genetic deletion (Trejo, Llorens-Martin, & Torres-Aleman, 2008), as well as immuno-neutralization (Trejo, Carro, & Torres-Aleman, 2001) of peripheral IGF-1 prevents the beneficial effects of exercise on hippocampus-dependent learning and memory.

In addition to IGF-1, NE signaling in the hippocampus could also contribute to BDNF elevations through a β-ADR-mediated mechanism (R. S. Duman, Heninger, & Nestler, 1997; R. S. Duman & Monteggia, 2006). Consistent with a role for the β-ADR, blockade of β-ADRs prevents the exercise-induced increase in BDNF (Ivy, Rodriguez, Garcia, Chen, & Russo-Neustadt, 2003) and the improved contextual conditioning typically observed following six weeks of wheel running (J. D. Van Hoomissen et al., 2004). The majority of the NE innervation to the hippocampus comes from the brain stem locus coeruleus (LC). We have observed that six weeks of wheel running increases ΔFosB/FosB protein in catecholaminergic neurons of the rat LC (Figure 7.1). Because ΔFosB/FosB accumulates following repeated neural activation, these data suggest that long-term wheel running repeatedly activates noradrenergic neurons in the LC. Consistent with these data, Garcia, Chen, Garza, Cotman, & Russo-Neustadt (2003) reported that N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine lesions of the LC reduce 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).

Together, these data suggest that IGF-1 and NE could improve hippocampus function through increases in BDNF, synaptic plasticity, and neuroprotection, resulting in enhanced context discrimination and anxiety reduction. A role for IGF-1 or NE in the hippocampus does not preclude the involvement of other brain regions in the improved context memory and context discrimination produced by exercise. The prefrontal cortex (PFC) is another region implicated in the pathophysiology and treatment of anxiety. Although exercise could affect the PFC directly, exercise-induced plasticity in the hippocampus could indirectly improve PFC function (Peters, Dieppa-Perea, Melendez, & Quirk, 2010). The hippocampus provides contextual information to the PFC, which may facilitate PFC-mediated cognitive appraisal of anxiety-producing situations in order to constrain inappropriate or exaggerated fear responses.

Unlearned anxiety

Models of unlearned anxiety in rodents involve exposure to a stimulus that elicits innate fear or conflict. Innate fear is often generated in rodents by exposure to an open field, light/dark box, or elevated plus maze. In these examples, the rodent experiences conflict between the drive for exploration and the fear of open or brightly lit spaces. In all of these cases, the fear response is an unlearned response to a natural threat.

The effects of exercise on anxiety in tests of unlearned anxiety remain equivocal. Exercise has been reported to produce no effects (Chaouloff, 1994; Mello, Benetti, Cammarota, & Izquierdo, 2009; Pietropaolo, Feldon, Alleva, Cirulli, & Yee, 2006), anxiogenic effects (R. S. Duman, 2002; Fuss, Ben Abdallah, Hensley, et al., 2010; Fuss, Ben Abdallah, Vogt, et al., 2010; Garcia-Capdevila et al., 2009; Grace et al., 2009), and anxiolytic effects (Binder, Droste, Ohl, & Reul, 2004; C. H. Duman, Schlesinger, Russell, & Duman, 2008; Salam et al., 2009; Trejo et al., 2008) in animal models of unlearned anxiety. The discrepancy is present in both sexes of rats and mice. Neither alterations in general activity (C. H. Duman et al., 2008), fatigue (C. H. Duman et al.,

2008; Salam et al., 2009), nor pain sensitivity (C. H. Duman et al., 2008; Falls et al., 2010; Fuss et al., 2009) seem to influence the effects of exercise in tests of unlearned anxiety. Other factors including type of exercise (i.e., forced vs. voluntary; Burghardt, Fulk, Hand, & Wilson, 2004; Dishman et al., 1996; Leasure & Jones, 2008), housing conditions (Dubreucq, Marsicano, & Chaouloff, 2011), duration of prior exercise (Burghardt et al., 2004), time of day of testing (Hopkins & Bucci, 2010), and duration of behavioral test (Binder et al., 2004), however, may partially explain the discrepancy in the literature. Several studies reporting anxiogenic effects of exercise in the open field and elevated plus maze tests, for example, perform relatively short, five-minute tests (Burghardt et al., 2004; R. S. Duman, 2002; Fuss, Ben Abdallah, Vogt, et al., 2010; Garcia-Capdevila et al., 2009). Binder et al. (2004), however, observed that the anxiogenic effect (reduced center exploration) of wheel running present during the first 10 minutes of an open field test was made up for during the final 20 minutes of the test. The cautious behavior displayed by exercised animals during the beginning of the anxiety test could reflect greater cognitive appraisal of the environment. Consistent with this interpretation are the observations that exercised, compared to sedentary, animals spend more time in the center (the border between the closed and open arms) of the plus maze (Garcia-Capdevila et al., 2009), a behavior that has been related to decision-making (Wall & Messier, 2001). Later in the test, when exercised animals seem to display anxiolytic profiles, prior exercise could facilitate a shift from risk assessment to exploration. This strategy of caution followed by enhanced exploration, although only revealed under appropriate testing conditions, could be an adaptive response to conflict that could enhance survival.

Another factor that influences the effect of exercise on unconditioned anxiety is the stress status of the animals. Indeed, Figure 7.2 suggests that the effect of exercise on unconditioned anxiety depends upon history of prior stressor exposure. In this experiment, male F344 rats remained sedentary or were allowed access to wheels for six weeks prior to exposure to uncontrollable tail shock stress (see Greenwood et al., 2003), which produces robust learned and unlearned anxiety (Baratta et al., 2007; Maier & Watkins, 1998). Twenty-four hours later, rats were exposed to a novel open field (Figure 7.2A) for five minutes. Results indicate that although wheel running does not alter the total movement in the open field (Figure 7.2B), wheel running does reduce the time spent in the center of the field during the five-minute test (Figure 7.2C). Uncontrollable stress also reduces the time spent in the center of the open field. Interestingly, the anxiogenic effect of stress is specific to sedentary rats. In physically active rats, exposure to stress actually increases the time spent in the center of the open field (Figure 7.2C). Van Hoomissen et al. (2011) reported a similar effect of exercise. This group reported that rats allowed to run in running wheels for three weeks following olfactory bulbectomy displayed a robust anxiolytic profile as measured by entries into the center of a novel environment (J. Van Hoomissen et al., 2011). Interestingly, it was only the exercised rats lacking an olfactory bulb who displayed the anxiolytic profile. Exercised sham rats behaved similarly to sedentary rats. Although the mechanisms underlying the interaction between exercise and stress in tests of unlearned anxiety are not yet clear, these data suggest that researchers should be especially sensitive to the stress status of their animals, as even subtle, unintentional differences in stress status may influence the effects of exercise on these tests. Until the behavioral effects of exercise in these tests are better characterized, it will be difficult to use these tests to investigate mechanisms underlying the effects of exercise on anxiety.

Figure 7.2 Effects of exercise on open field behavior.

Stress-induced anxiety

In addition to demonstrating that the behavioral effects of exercise in animal models of unlearned anxiety depend on the history of stressor exposure, the data in Figure 7.2 also provide an example of the powerful protective effect of exercise against stress-induced anxiety. Moreover, Figure 7.2 and prior data (Greenwood, Foley, Burhans, et al., 2005; Greenwood et al., 2003) suggest that the anxiolytic effects of exercise may be even more likely revealed following exposure to an event that can facilitate the development of anxiety, such as stressor exposure. Indeed, human data suggest the anxiolytic effects of exercise are more robust in individuals who are most susceptible to anxiety (Smits, Tart, Rosenfield, & Zvolensky, 2011). It may therefore be most appropriate to investigate the anxiolytic effects of exercise in animal models of anxiety following exposure to a manipulation (be it genetic, pharmacological, or environmental) that is known to lead to anxiety-like behaviors in sedentary organisms. One such manipulation is exposure to stress. Indeed, stressor exposure is an important causal factor in the development of human anxiety disorders. Animal models utilizing exposure to stressors may have the greatest potential for identification of the neurobiological mechanisms underlying the anxiolytic effects of exercise.

Behavioral effects of exercise on animal models of stress-induced anxiety

It is now well established that the behavioral consequences of stress that resemble anxiety are sensitive to physical activity status. Sedentary rats exposed to an uncontrollable stressor display behaviors that resemble symptoms of human anxiety, including social avoidance, exaggerated conditioned fear, and interference with instrumental learning (Christianson et al., 2008; Greenwood et al., 2003; Maier, 1990). Rats and mice allowed access to running wheels prior to uncontrollable stressor exposure are protected against later deficits in instrumental learning measured in the shuttle box escape task (Dishman et al., 1997; C. H. Duman et al., 2008; Greenwood, Foley, Burhans, et al., 2005; Greenwood et al., 2003; Greenwood et al., 2007), as well as the anxiety measured by social exploration (Greenwood et al., 2012) and conditioned fear (Greenwood, Foley, Burhans, et al., 2005; Greenwood et al., 2003; Greenwood et al., 2007).

Exercise protection against stress-induced anxiety extends beyond uncontrollable stressors and psychological stressors in general. Using a variety of anxiety tests including open field, light/dark box, the hole-board test, shock-probe defensive burying, and acoustic startle, exercise has been observed to prevent anxiety elicited by 24 hours of sleep deprivation (Vollert et al., 2011), oxidative stress (Salim et al., 2010), experimentally induced colitis (Kasimay et al., 2006), acute

administration of a β-carboline (Sciolino, Dishman, & Holmes, 2012), a selective serotonin (5-HT) reuptake inhibitor (Greenwood, Strong, Brooks, & Fleshner, 2008), a non-selective 5-HT_2 receptor agonist (Fox, Hammack, & Falls, 2008), and a selective 5-HT_{2C} receptor agonist (Greenwood, Strong, et al., 2012). The protective effect of exercise against stress-induced anxiety thus appears to be a relatively consistent observation that extends across many stressors and anxiety tests.

Potential mechanisms

Mechanisms that could contribute to the protective effect of exercise against stress-induced anxiety include changes in brain monoamines (Dishman et al., 1997; Greenwood & Fleshner, 2011; Greenwood et al., 2005b) and circuits involved in reward (Greenwood et al., 2011) or entrainment of circadian rhythms (Edgar & Dement, 1991; Solberg, Hortaon, & Turek, 1999), and enhanced neurotrophic (Russo-Neustadt & Chen, 2005), anti-inflammatory (Cotman et al., 2007; Gleeson et al., 2011), or antioxidant (Salim et al., 2010; Vollert et al., 2011) support. The literature on the effects of exercise on these systems is rather difficult to interpret due to the use of various exercise paradigms (i.e., forced swimming, treadmill training, and wheel running), which vary in their degree of stress, in addition to exercise duration, intensity, pattern, and controllability. Because many of these systems are also sensitive to stress, it has been difficult to separate the effects of stress from those of exercise, per se. This is especially true of forced exercise paradigms such as swimming or treadmill training, which are inherently stress-evoking (Brown et al., 2007; Moraska, Deak, Spencer, Roth, & Fleshner, 2000). Moreover, a recent study indicates that 6 weeks of treadmill training was unable to prevent stress-induced anxiety measured with conditioned fear (Greenwood, Spence, et al., 2012). For these reasons, future studies would be well served to focus on the effects of voluntary exercise, or at least a forced exercise paradigm demonstrated to prevent stress-induced anxiety (Greenwood, Spence, et al., 2012), on central changes associated with anxiety reduction.

We have been interested in the effects of voluntary exercise on the central 5-HT system. The focus on 5-HT is appropriate, given the involvement of 5-HT in reward (Hayes & Greenshaw, 2011), circadian entrainment (Meyer-Bernstein & Morin, 1996), and anxiety (Graeff, Guimaraes, De Andrade, & Deakin, 1996; Lowry, Johnson, Hay-Schmidt, Mikkelsen, & Shekhar, 2005). Moreover, accumulating data indicate that an increase in 5-HT is causal in anxiety and is critical for the social avoidance, exaggerated fear conditioning, and interference with instrumental learning produced by uncontrollable stress (Maier & Watkins, 2005). Exercise produces neuroplasticity in the central 5-HT system at multiple levels including (1) brain regions that modulate 5-HT activity during stressor exposure, (2) 5-HT cell body regions, such as the dorsal raphe nucleus, and (3) 5-HT projection sites, such as reduced expression or sensitivity of postsynaptic 5-HT receptors in brain regions critical for the expression of stress-induced anxiety. We have presented evidence supporting a role for each of these possibilities in the protective effect of exercise against stress-induced anxiety (Greenwood & Fleshner, 2011; Greenwood, Foley, Burhans, et al., 2005; Greenwood, Foley, Day, et al., 2005; Greenwood et al., 2003, 2012). Together, available data support the idea that limiting the behavioral impact of acute increases in 5-HT during stressor exposure contributes to the protection against stress-induced anxiety produced by exercise.

Exercise-induced plasticity in the central 5-HT system could contribute to anxiolytic effects of exercise in several types of anxiety. For example, 5-HT can modulate BDNF in the hippocampus, where 5-HT2 receptor activation contributes to stress-induced reductions in BDNF (Vaidya, Terwilliger, & Duman, 1999). Voluntary exercise prevents the reduction in

BDNF mRNA and protein in the hippocampus produced by stressor exposure (Adlard & Cotman, 2004; Greenwood et al., 2007), an observation that would be expected if exercise constrained stress-induced activation of 5-HT neurons or reduced sensitivity or expression of 5-HT2 receptors in the hippocampus. The effects of exercise on 5-HT and neurotrophic systems might, therefore, interact to produce anxiolytic effects under a variety of conditions (Figure 7.1).

Conclusions and future directions

Exercise is anxiolytic in tests of context discrimination and stress-induced anxiety. Mechanisms underlying the anxiolytic effects of exercise could include plasticity in neurotrophic and/or 5-HT systems that modulate learning and memory processes and behavioral responses to stress. The behavioral effects of exercise on animal models of unlearned anxiety are not yet clear, but seem to depend upon the history of stressor exposure. Investigators, therefore, should be especially attentive to the stress status of their animals when investigating mechanisms underlying the anxiolytic effects of exercise. This applies especially to the use of forced exercise paradigms such as swimming or treadmill training, which inherently introduce aspects of repeated stress. The mechanisms by which the experience of exercise is communicated to the brain to reduce anxiety could include peripheral IGF-1 or central NE, and is an important area of future inquiry. To identify these mechanisms, future studies should utilize exercise paradigms demonstrated to produce significant behavioral effects in animal models of anxiety.

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