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Exercise, Learned Helplessness, and the Stress-Resistant Brain

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Abstract Exercise can prevent the development of stress-related mood disorders, such as depression and anxiety. The underlying neurobiological mechanisms of this effect, however, remain unknown. Recently, researchers have used animal models to begin to elucidate the potential mechanisms underlying the protective effects of physical activity. Using the behavioral consequences of uncontrollable stress or "learned helplessness" as an animal analog of depression- and anxiety-like behaviors in rats, we are investigating factors that could be important for the antidepressant and anxiolytic properties of exercise (i.e., wheel running). The current review focuses on the following: (1) the effect of exercise on the behavioral consequences of uncontrollable stress and the implications of these effects on the specificity of the "learned helplessness" animal model; (2) the neurocircuitry of learned helplessness and the role of serotonin; and (3) exercise-associated neural adaptations and neural plasticity that may contribute to the stress-resistant brain. Identifying the mechanisms by which exercise prevents learned helplessness could shed light on the complex neurobiology of depression and anxiety and potentially lead to novel strategies for the prevention of stress-related mood disorders.

Keywords Exercise · Depression · Stress · Wheel running · Serotonin

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Introduction

It is now well accepted that habitual physical activity significantly reduces the incidence and severity of stress-related mood disorders, such as depression and anxiety. The effectiveness of physical activity on reducing symptoms of depression and anxiety disorders has been extensively reviewed (Dunn et al. 1991, 2001; Salmon 2001; Brosse et al. 2002; Suh et al. 2002; Morgan 1985; Paluska and Schwenk 2000; Fox 1999; Scully et al. 1998; Martinsen 1990a, b; Mutrie 2000; Martinsen and Morgan 1997; Lawlor and Hopker 2001; North et al. 1990). The protective effect of exercise against stress-related mood disorders occurs regardless of exercise type (aerobic or resistance training) (Martinsen 1990a; Martinsen et al. 1989; Singh et al. 1997), and can be as effective as conventional pharmacotherapy (Mutrie 2000; Babyak et al. 2000; Blumenthal et al. 1999; Martinsen 1994). The effect size of the protective effect of exercise against depression or anxiety is large and, in fact, is equal to that of the protective effect of exercise against cardiovascular disease (North et al. 1990). Although it is clear that exercise can prevent the development of depression and anxiety, the underlying mechanisms of this effect remain unresolved. Recently, researchers have increasingly turned to animal models in order to elucidate potential mechanisms underlying the protective effects of physical activity. Using the behavioral consequences of uncontrollable stress (i.e., learned helplessness) as an animal analog of depression- and anxiety-like behaviors in rats, for example, we have begun to investigate factors that could be important for the antidepressant and anxiolytic properties of exercise. The current review will first describe the effect of exercise on the behavioral consequences of uncontrollable stress and the implications of these effects on the specificity of the

"learned helplessness" animal model. We will then describe the neurocircuitry of learned helplessness and the role of serotonin (5-HT). Finally, we will propose several exercise-associated neural adaptations that could contribute to the stress-resistant brain.

Wheel Running and Animal Models of Stress-Related Mood Disorders

Similar to the beneficial effects of exercise in humans, increasing the physical activity status of laboratory rodents prevents the immergence of depression- and anxiety-like behaviors in animal models. A useful way to manipulate physical activity status in rodents is to allow them voluntary access to running wheels. Adult, male Fischer 344 rats that are allowed access to running wheels will choose to run about 2.0 km/night (Greenwood et al. 2005a, b), but distances vary depending on strain. Voluntary running avoids potential confounding effects of forced exercise (e.g., treadmill training or swimming) such as adaptation to a chronic stressor (Moraska et al. 2000). In fact, voluntary wheel running is rewarding (Werme et al. 2002) and rats allowed to run will prefer to spend time in a chamber associated with the aftereffects of wheel running (Lett et al. 2000). It is difficult to define wheel running in terms of a specific type and intensity of exercise. Wheel running does not produce as great of a biochemical "training" effect as does some forced treadmill training protocols. This is indicated by the inability of at least 4–8 weeks of wheel running to increase muscle citrate synthase (Kennedy et al. 2005) or succinate dehydrogenase (Dunn et al. 1996) activity. In contrast, treadmill training increases muscle enzymatic capacity (Moraska et al. 2000; Dunn et al. 1996; Dishman et al. 2000); a classic biochemical marker of aerobic training. Wheel running, nevertheless, does result in a number of physiological effects indicative of moderate aerobic exercise including elevations in mean corpuscular content of hemoglobin and an improvement of LDL/HDL ratio (Kennedy et al. 2005). In terms of the protective effects of wheel running against stress-related behaviors, the specific intensity of the exercise may be, in any case, less important than the duration of running. As will become clear later, wheel running prevents the development of depression- and anxiety-like behavioral consequences of stressor exposure and, in fact, may be even more protective than forced exercise which fails to alter behavior in some models (Burghardt et al. 2004; Chaouloff 1994). Moreover, a dose–response relationship between exercise and an antidepressant effect has yet to be identified in humans (Dunn et al. 2001).

An array of behavioral tests has revealed that voluntary wheel running can prevent the development of depression- and anxiety-like behaviors. For example, 4 or more weeks of wheel running reduces anhedonic behaviors, including reductions in copulatory behavior and sucrose preference, induced by chronic unpredictable stress (Zheng et al. 2006) or olfactory bulbectomy (Chambliss et al. 2004). Wheel running also is antidepressant in the Flinders Sensitive ratline (Bjornebekk et al. 2005, 2006), reduces immobility in the forced swim test (Solberg et al. 1999), and elicits typical anxiolytic responses in the elevated plus maze and light and dark box (Binder et al. 2004).

We have focused our work on the effects of wheel running on the learned helplessness model of stress-related mood disorders. Physiological and behavioral consequences of exposure to uncontrollable, but not controllable, stressors are called "learned helplessness" (Maier and Seligman 1976; Seligman and Beagley 1975), or "behavioral depression" (Weiss et al. 1981). Learned helplessness effects are dependent on the uncontrollability of the stressor and do not occur if the stressor is controllable or escapable. Behavioral consequences of uncontrollable stress that depend on the uncontrollability of the stressor include "exaggerated" freezing (anxiety) and deficits in learning to escape from escapable foot shocks in a shuttle box (the shuttle box escape deficit; see Maier and Watkins (1998) for a review). Behavioral effects of uncontrollable stress can be sensitive to anxiolytic (Maier et al. 1994; Drugan et al. 1984) and antidepressant (Sherman et al. 1982; Shirayama 2002) drugs, and have been argued to represent animal analogs of human anxiety and depression (Maier and Watkins 1998; Maier 1984; Petty et al. 1997; Willner 1986; Weiss and Kilts 1998). It is not problematic that learned helplessness shares features of both depression and anxiety because stress is a primary causal factor in both disorders (Kendler et al. 1999; van Praag 2005), depression and anxiety are often comorbid (Gorman 1996; Pollack 2005), and exercise reduces the incidence of both.

Rats allowed 6 weeks of voluntary access to running wheels prior to exposure to a series of uncontrollable tail shocks are protected against the exaggerated fear and shuttle box escape deficits that are typically present 24 h following uncontrollable tail shock exposure. The protective effects of wheel running against learned helplessness are dependent on the duration of prior wheel running (Greenwood et al. 2005a), and are not due to general activating effects of exercise on motor activity. In fact, prior exercise has actually been shown to decrease spontaneous movement during exposure to a novel environment (Binder et al. 2004).

Investigations into the mechanisms by which wheel running prevents learned helplessness have stimulated novel insights into the neurobiology of stress-related mood disorders and factors that could facilitate stress resistance. Before potential mechanisms by which exercise could

prevent learned helplessness are discussed, it is necessary to understand the specificity of learned helplessness phenomena and what is meant by "learned helplessness." This will avoid any confusion with past and future work dealing with the effects of exercise or other antidepressant strategies on learned helplessness or learned helplessness-like effects.

Exercise and the Specificity of Learned Helplessness

Since its inception, the phenomenon of "learned helplessness" has become almost synonymous with the failure to escape or avoid shock in a shuttle box. However, in their critical review of learned helplessness, Maier and Watkins (2005) point out that escape deficits, per se, do not define learned helplessness. Instead, learned helplessness is the constellation of behavioral consequences of uncontrollable stress that (1) depend on the uncontrollability of the stressor and (2) are "trans-situational," i.e., they occur in an environment that the subject views as being distinct from that in which the original stressor experience occurred (Maier et al. 1969). The common practice of referring to all shuttle box escape deficits as "learned helplessness" has created real confusion in the literature regarding certain features and neurobiological mechanisms of the behavioral consequences of uncontrollable stress.

The foremost example of this confusion is the time course by which uncontrollable stress-induced escape deficits are thought to persist following stressor exposure. Maier and colleagues have reported that shuttle box escape deficits produced by uncontrollable tail shock are maximal 24 h after stressor exposure but are gone by 72 h (Maier 2001; Maier and Watkins 2005). In contrast, Greenwood et al. (2007a), Duman and colleagues (Shirayama 2002; Malberg 2003) and many others have reported much longer lasting escape deficits following uncontrollable foot shock compared with uncontrollable tail shock. The differences between these methods may seem trivial. Indeed, many physiological and behavioral consequences of tail shock versus foot shock are similar. It has been suggested that differences in the persistence of the escape deficits following uncontrollable tail shock versus foot shock is not due to subtle differences between the anatomical locations of shock delivery but is instead due to the different contextual relationships between the stressor and the testing environments (Maier and Watkins 2005). Rats that are given foot shock in the shuttle box learn to associate the shuttle box environment with shock. When rats are placed back into the shuttle box for later testing, it is likely that the shuttle box environment triggers fearful memories of previously administered foot shocks. In this case the contextual relationship would be similar and the resulting fear memory could contribute to the long lasting escape deficits observed following uncontrollable foot shock. In the case of tail shock that is administered to the rats in Plexiglas tubes, no such memories of the shuttle box would be present. The contextual relationship between the uncontrollable shocks and the testing environment would be different, and the escape deficit would be more transient. Indeed, prior work indicates that minimal fear transfers from the tail shock apparatus to the shuttle box (Maier 1990; Greenwood et al. 2003a).

To determine if the time-course of uncontrollable stress-induced escape deficits are dependent on the contextual relationship between the stress and testing environments, we exposed adult, male, Fischer 344 rats to either no stress or a series of 100, 1.6 mA, 5 s, uncontrollable tail shocks (1 min random intertrial-intervals) while being restrained in a tail shock tube placed either (1) on a stainless-steel lab bench or (2) into the shuttle box in which later behavioral testing was to occur. The tail shock tubes were modified to allow the rats' front paws to extend from the tubes and make contact with the grid floor of the shuttle box during tail shock presentation. One week later, a time point at which contextually distinct stress-induced escape deficits are no longer present, rats were placed into shuttle boxes and freezing (as a measure of contextually conditioned fear) and fixed ratio-2 (FR-2) escape learning (during which rats are required to cross through the shuttle box door twice in order to escape shock) were assessed as described previously (Greenwood et al. 2003a, 2007a). Using a random sampling procedure, freezing was scored every 8 s as either freezing or not freezing during the first 6 min after placement of the rats into the shuttle box and before administration of any foot shock. During escape trials, shocks were automatically terminated if an escape response did not occur within 30 s. In these cases, 30 s escape latencies were assigned.

The results are shown in Fig. 1. As expected, non-stressed rats did not freeze when placed into the shuttle box and easily learned to escape during the 25 FR-2 escape trials. Rats exposed to tail shock on the lab bench also displayed little freezing when placed into the shuttle box, indicating that minimal fear transferred from the tail shock tube to the shuttle box under these conditions. Consistent with prior reports (Maier 2001; Maier and Watkins 2005), tail shock on the lab bench 1 week prior to behavioral testing did not interfere with escape learning. In contrast, prior exposure to tail shock in the shuttle box resulted in a significant expression of freezing (representative of a fear memory of cues present in the shuttle box) and, similar to effects of uncontrollable foot shock, interfered with the rats' ability to escape. These data clearly indicate that the differential temporal effects of uncontrollable stress are likely due to the contextual relationship between the stressor and testing

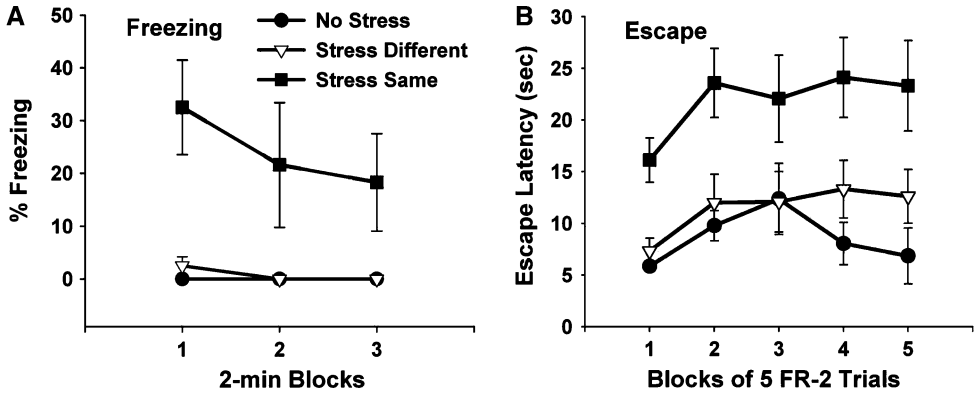

Fig. 1 The effect of varying contextual relationships between the stressor and testing environments on later freezing and shuttle box escape performance. Sedentary, adult, male, Fischer 344 rats were either exposed to no stress ($n = 7$) or to a series of 100 uncontrollable tail shocks (1.5 mA, 5 s duration, 60 s average ITI) while being restrained in tail shock tubes. Tubes were either placed on a lab bench (stress different; $n = 8$) or inside the shuttle box in which later behavioral testing was to take place (stress same; $n = 8$). The tubes were modified to allow the rats' front paws to make contact with the grid floor of the shuttle box during tail shock exposure. One week later rats were placed into shuttle boxes for assessment of conditioned freezing and fixed ratio-2 (FR-2) escape performance, during which rats were required to cross through the shuttle box door twice in order to terminate foot shock. (**a**). Prior tail shock in the shuttle box (stress same), but not on the lab bench (stress different), elicited significant conditioned freezing behavior relative to non-stressed rats. These results were confirmed with repeated measures ANOVA which revealed a significant effect of group ($F(2, 20) = 5.8$; $P < .05$). (**b**) Prior tail shock in the shuttle box (stress same), but not on the lab bench (stress different), interfered with FR-2 escape learning. These results were confirmed with repeated measures ANOVA which revealed a significant effect of group ($F(2, 20) = 9.12$; $P < .05$). The stress same group differed from the no stress and the stress different groups during all 5 trial blocks

environments and not the type of shock (i.e., tail shock versus foot shock). Thus, consideration of the trans-situational component of the original definition of learned helplessness is critical to our understanding of the behavioral consequences of uncontrollable stress. This is important because it is unlikely that prior studies reporting long-lasting escape deficits produced by uncontrollable stress were measuring learned helplessness effects, per se, because the trans-situational component of the definition of learned helplessness was not satisfied. One method of assessing escape learning may not necessarily be better or worse than another in terms of the utility of the escape deficit as a model of depressive- or anxiety-like behavior. The fact that the persistence of uncontrollable stress-induced escape deficits are dependent on the contextual relationship between the stressor and testing environments simply illustrates the subtle differences in the ways that uncontrollable stress can lead to deficits in escape learning, some of which are learned helplessness, and some of which are not.

Neurobiological mechanisms underlying learned helplessness will be described below, but it is relevant here that Fig. 1 is consistent with the suggestion (Maier and Watkins 2005) that, while learned helplessness is independent of fear, the long-lasting escape deficits induced by uncontrollable stress may depend on fear conditioning. To determine if a testing environment is sufficiently different from a stressor environment to eliminate potential conditioning effects, one could simply score freezing as a measure of fear memory prior to commencement of escape trials, as was done in the study just described and as Maier and Watkins (2005) have previously suggested.

If the time-course of uncontrollable stress-induced escape deficits depends on the contextual relationship between the stressor and the testing environments, then perhaps the effect of exercise on uncontrollable stress-induced escape deficits also varies depending on this relationship. In fact, given that (1) conditioned freezing could contribute to the escape deficits when the stressor and testing environments are similar, and (2) wheel running is known to increase contextually conditioned freezing (van Hoomissen et al. 2004; Burghardt et al. 2006), one might actually predict that wheel running would fail to block the shuttle box escape deficit when the stressor and testing environments are the same. To determine if the protective effect of wheel running against uncontrollable stress-induced escape deficits is dependent on the contextual relationship between the stressor and testing environments, rats either remained sedentary or were allowed voluntary access to running wheels for 6 weeks. Rats were then either exposed to uncontrollable tail shock following our standard procedures (on the lab bench; stress different) or uncontrollable foot shocks in the same shuttle box in which assessment of freezing and escape behavior was to occur 24 h later (stress same).

The results from this experiment are shown in Fig. 2. We have already demonstrated that wheel running, in the absence of any stressor, affects neither freezing nor escape (Greenwood et al. 2003a, 2005a). Therefore, exercised

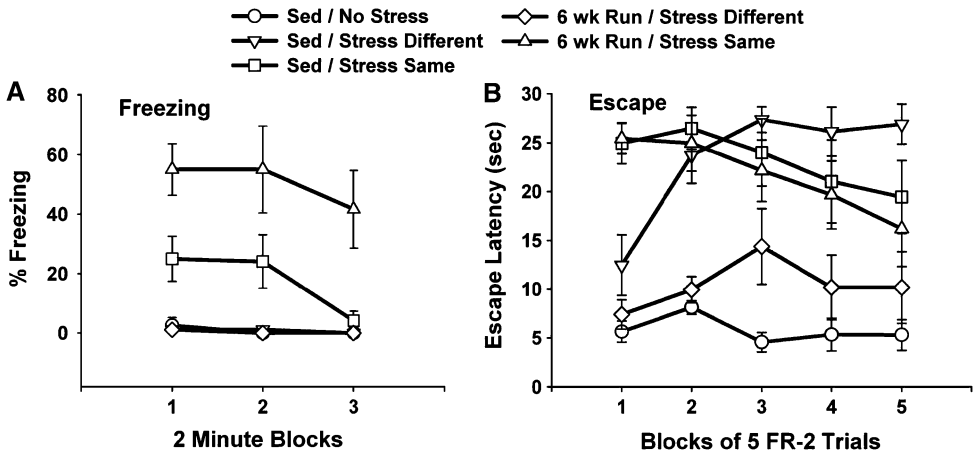

Fig. 2 The protective effect of wheel running against the behavioral consequences of uncontrollable stress depends on the contextual relationship between the stress and testing environments. Rats either remained sedentary or were allowed voluntary access to running wheels for 6 weeks (6 wk Run) prior to no stress or uncontrollable shocks on the lab bench (stress different) or in the shuttle box (stress same). Twenty-four hours after stressor exposure, rats were placed into shuttle boxes for assessment of conditioned freezing and fixed-ratio 2 (FR-2) escape learning. (**a**) Sedentary, non-stressed rats ($n = 4$) displayed no freezing behavior in the shuttle boxes. Prior uncontrollable shocks in a different environment did not elicit any freezing behavior in sedentary ($n = 6$) or physically active ($n = 6$) rats. In contrast, prior uncontrollable shocks administered in the shuttle boxes elicited freezing behavior in both sedentary ($n = 8$) and physically active ($n = 8$) rats and this freezing was potentiated by prior wheel running. These results were confirmed with repeated measures ANOVA that revealed a reliable main effect of group ($F(4, 27) = 11.73$; $P < .0001$). (**b**) Sedentary, non-stressed rats easily learned to escape during FR-2 trials. Prior uncontrollable shocks, regardless of location, interfered with sedentary rats' ability to learn to escape. In contrast, only uncontrollable stress in the same environment interfered with physically active rats' ability to escape. Physically active rats that received uncontrollable shocks in a different environment were protected against the stress-induced escape deficit. Repeated measures ANOVA confirmed these results and revealed significant main effects of Group ($F(4, 27) = 8.9$; $P < .0001$), trial block ($F(4, 108) = 3.4$; $P < .05$), and a reliable interaction between group and trial block ($F(16, 108) = 3.9$, $P < .0001$). The sedentary and wheel run/stress same groups differed from the sedentary/no stress and the wheel run/stress different groups during all escape trial blocks except the fifth block during which the wheel run/stress same and wheel run/stress different groups did not differ. The sedentary/stress different group differed from the sedentary/no stress and the wheel run/stress different groups during the second through fifth trial blocks.

non-stressed rats were not included in the study. Sedentary non-stressed rats displayed no freezing behavior and had no trouble escaping from FR-2 escape trials. Freezing scores during the first 6 min after placement into the shuttle boxes on the day of testing are shown in Fig. 2a. Prior uncontrollable shocks in the same environment, but not in the different environment, elicited significant conditioned freezing. As expected, physically active rats displayed greater freezing compared to sedentary counterparts. Results of the escape trials are shown in Fig. 2b. When the environments were different, 6 weeks of prior wheel running blocked the stress-induced escape deficit. When the environments were the same, however, wheel running had no effect. These data clearly demonstrate the protective effect of wheel running against uncontrollable stress-induced escape deficits is dependent on the contextual relationship between the stressor and testing environments. Thus, it appears that the protective effect of exercise against stress-induced shuttle box escape deficits is only revealed when the stressor and testing environments are sufficiently different. If the environments are the same, then something, perhaps the presence of conditioned fear, overshadows the protective effect of exercise.

It is interesting that wheel running facilitates contextual fear conditioning (an effect typically associated with anxiety) when exercise in humans is clearly anxiolytic. However, it is important to point out here that when wheel running occurs for 6 weeks after uncontrollable stress, wheel running no longer increases freezing elicited by re-exposure to the stressor environment (Greenwood et al. 2007b). In fact, in this case wheel running actually facilitates within-session extinction of fear. Additionally, the escape deficit present in the same environment in which prior uncontrollable stress took place can also be reversed by 6 weeks of wheel running (Greenwood et al. 2007b). This reversal of the long-lasting escape deficit could represent a therapeutic effect of exercise that is similar to reported therapeutic effects of exercise in humans. Using this model, we are just beginning to explore the mechanisms underlying the therapeutic effects of exercise.

In summary, it is clear from the behavioral data that exposure to an uncontrollable stressor produces (1) rapid but transient interference with escape learning in different environments (a learned helplessness effect) and (2) rapid and long-lasting interference with escape learning in similar environments. Prior wheel running prevents learned

helplessness (different environment) but does not prevent the uncontrollable stress-induced escape deficit when behavioral testing occurs in the same environment in which stress occurred. Thus, wheel running prevents specifically "learned helplessness" behaviors. A great deal is known about the neurocircuitry of learned helplessness in sedentary animals. The following will describe our current understanding of this neurocircuitry, and how wheel running-induced adaptations in this neurocircuitry could contribute to the protective effects of exercise.

Critical Role for Dorsal Raphe Serotonergic Neurons in the Neurocircuitry of Learned Helplessness

Evidence suggests an important role for 5-HT neurons in the dorsal raphe nucleus (DRN) in mediating learned helplessness (see Maier and Watkins 2005, for reviews). The DRN is a midline brainstem structure that contains a high concentration of 5-HT neurons that provide 5-HT to higher brain centers via multiple fiber tracts. The DRN has been described as containing distinct subdivisions based on the distribution of 5-HT neurons, afferent and efferent innervation, unique receptor expression, and responses to various neurotransmitters and neuropeptides (Clark et al. 2006; Abrams et al. 2004; Lowry 2002; Jacobs and Azmitia 1992; Staub et al. 2006). 5-HT neurons in the DRN have long been associated with depression (Ressler and Nemeroff 2000; Maudhuit et al. 1995; Coppen and Doogan 1988; Owens and Nemeroff 1994), anxiety (Anderson and Mortimore 1999; Ninan 1999; Abrams et al. 2005; Lowry et al. 2005), and behavioral responses to stress (Lucki 1998; Graeff et al. 1996; Maier et al. 1993). The DRN projects to structures involved in fear, anxiety, and depression, such as the cortex, amygdala, periaqueductal grey (PAG), and locus coeruleus (LC) (Lowry 2002; Peyron et al. 1996, 1998; Kazakov et al. 1993). The DRN receives reciprocal projections from these regions and others including the bed nucleus of the stria terminalis (BST) (Dong et al. 2001), a region particularly important in responses to unpredictable and uncontrollable events (Walker et al. 2003).

Although the effect of laboratory stressors on DRN 5-HT neurons can vary depending on the type of stressor (Kirby et al. 1997), work lead primarily by Steven F. Maier and colleagues indicates that DRN 5-HT neurons are particularly sensitive to stressor controllability, thus implicating DRN 5-HT neurons in learned helplessness. A neural circuit involving the amygdala, BST, and LC is reactive to uncontrollable stressors (Greenwood et al. 2003b, 2005a; Takase et al. 2005) and neurons in these regions that project to the DRN could stimulate DRN 5-HT neurons. This is particularly important because a growing body of evidence suggests that the behavioral consequences of uncontrollable stress are due to hyperactivation of 5-HT neurons in the DRN. Uncontrollable stressors activate DRN 5-HT neurons more than controllable stressors as evidenced by the observations that uncontrollable shocks illicit (1) greater c-Fos induction in DRN 5-HT neurons (Grahn et al. 1999), and (2) exaggerated 5-HT release within the DRN (Maswood et al. 1998; Amat et al. 2001), relative to an equal number of controllable shocks of the same intensity and duration.

Hyperactivation of the DRN is hypothesized to produce sensitization of the DRN that persists for 24–72 h. There is evidence, for example, that 24 h after uncontrollable shocks, but not controllable shocks, there is exaggerated 5-HT release in DRN projection sites such as the basolateral amygdala (Amat et al. 1998a) and ventral hippocampus (Amat et al. 1998b) during exposure to mild foot shocks. Exaggerated 5-HT release in DRN projection sites during behavioral testing 24 h after uncontrollable stress could contribute to the behavioral consequences of uncontrollable stress. Indeed, 5-HT in two DRN projection sites, the amygdala and the PAG, can increase freezing and interfere with escape performance, respectively (Graeff et al. 1993, 1996, 1997).

Hyperactivation and sensitization of the DRN are necessary for learned helplessness to occur. DRN lesions (Maier et al. 1993) or pharmacological inhibition of the DRN (Maier et al. 1994, 1995b), either during uncontrollable stress or later behavioral testing, prevents both the exaggerated freezing and the deficits in shuttle box escape learning typically observed 24 h following uncontrollable tail shocks. Importantly, the rats in these experiments had never been introduced to the shuttle boxes, or anything resembling the shuttle boxes, prior to behavioral testing. The fact that the shuttle boxes were novel in these experiments means that manipulations that inhibit the DRN prevent and reverse specifically learned helplessness. Indeed, if the original uncontrollable stressor and later assessment of escape performance occur in identical environments; then escape deficits are neither prevented nor reversed by pharmacological inhibition of the DRN with low-dose, systemic 8-OH-DPAT (Maier and Watkins 2005). Thus, not only does the time course of the escape deficit and the sensitivity to modulation by exercise differ depending on the contextual relationship between the stressor and testing environments, so do the underlying neural mechanisms.

Not only is activation of DRN 5-HT neurons necessary for learned helplessness, manipulations that increase central 5-HT (Brown et al. 1982) or activity of 5-HT neurons, in the absence of stress, are sufficient to produce behaviors resembling those produced by uncontrollable stress. For example, pharmacological activation of the DRN with the

benzodiazepine receptor inverse agonist DMCM produces exaggerated freezing and interferes with shuttle box escape learning 24 h later (Maier et al. 1995a). The increase in extracellular 5-HT in the DRN is likely to be a critical factor in the mechanisms by which pharmacological manipulations or uncontrollable stressors alter behavioral responding. Simply elevating extracellular 5-HT in the DRN by microinjecting the selective-5-HT-reuptake inhibitor (SSRI) citalopram into the DRN is sufficient to dose–responsively interfere with shuttle box escape performance 24 h later (Fig. 3).

The mechanisms by which uncontrollable stressors sensitize 5-HT neurons in the DRN are currently unknown but evidence points to a role for the 5-HT1A inhibitory autoreceptor. 5-HT1A receptors are autoreceptors in the DRN and postsynaptic heteroceptors on non-serotonergic neurons in other brain sites. In the DRN, 5-HT1A autoreceptors are located on the soma and dendrites of 5-HT neurons and are potent inhibitors of 5-HT neural activity and 5-HT release (Stamford et al. 2000). 5-HT1A autoreceptors, but not post-synaptic 5-HT1A receptors, are rapidly regulated by stimuli such as ligand binding or stress. For example, Riad and colleagues have demonstrated that systemic administration of either an SSRI or the 5-HT1A agonist 8-OH-DPAT rapidly internalize 5-HT1A autoreceptors in the DRN but not post-synaptic 5-HT1A receptors in the hippocampus (Riad et al. 2001, 2004). It is therefore possible that the hyperactivation of DRN 5-HT neurons, and the subsequent exaggerated release of 5-HT in the DRN, during uncontrollable, but not controllable, stressors sensitizes DRN 5-HT neurons to subsequent stressors by internalizing 5-HT1A autoreceptors in the DRN. Indeed, desensitization of 5-HT1A autoreceptors in the DRN following uncontrollable, but not controllable, tail shock has been documented by a reduction in receptor ligand ((^{3}H)8-OH-DPAT) binding to the 5-HT1A autoreceptor (Short et al. 2000). Transient uncontrollable stress-induced desensitization of 5-HT1A autoreceptors in the DRN would remove an important source of 5-HT neuronal inhibition, thus sensitizing DRN 5-HT neurons and producing learned helplessness behaviors 24 h later.

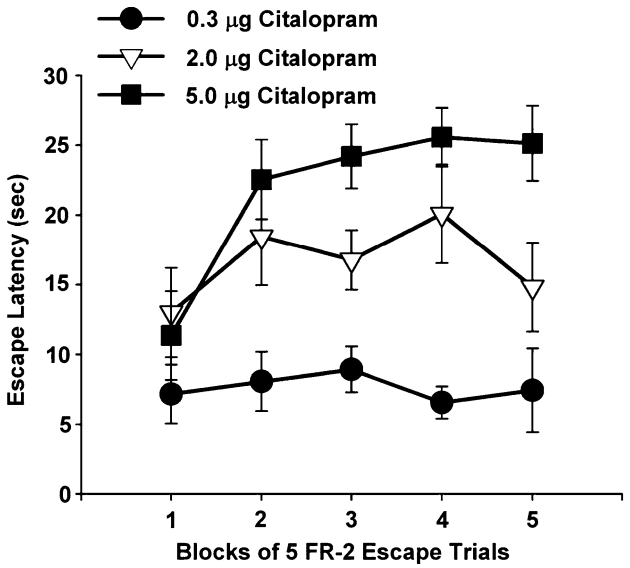

Fig. 3 Effect of citalopram microinjected into the dorsal raphe nucleus on escape performance. Sedentary rats were fitted with stainless steel guide cannula aimed just above the dorsal raphe nucleus (5.1 mm ventral and 8.0 mm caudal from bregma based in Paxinos and Watson (1998) following previously published protocols (Greenwood et al. 2007a)). After 2 weeks of recovery, rats received intra-dorsal raphe nucleus injection (1.0 μl) of either 0.3 ($n = 6$), 2.0 ($n = 8$), or 5.0 ($n = 8$) μg of citalopram. The injector extended 0.8 mm beyond the ventral tip of the guide cannula to allow the drug to be injected into the dorsal aspect of the DRN. Twenty-four hours after injection, rats were placed into shuttle boxes for assessment of fixed ratio-2 (FR-2) escape performance. Citalopram dose–responsively interfered with escape performance. Repeated measures ANOVA revealed significant main effects of group ($F(2, 19) = 12.9$, $P < .05$), trial block ($F(4, 76) = 4.63$, $P < .05$), and a significant interaction between group and trial block ($F(8, 76) = 2.13$, $P < .05$). Group sizes given are those remaining after exclusion of rats with misplaced cannulae. The 2.0 and 5.0 μg groups differed from the 0.3 μg group during the second through fifth trial blocks. The 2.0 and 5.0 μg groups differed from each other during the third and fifth trial blocks

It may seem counterintuitive that an increase in 5-HT release can lead to learned helplessness behaviors, especially considering that an increase in 5-HT neurotransmission seems to be important for the therapeutic effects of antidepressant drugs (O'Leary et al. 2007; Delgado et al. 1999). Chronic (several weeks) administration of antidepressants, however, is required for therapeutic benefits (Quitkin et al. 1996) even though antidepressants such as SSRIs increase extracellular 5-HT immediately (Hervas et al. 2000). In fact, increases in anxiogenic and depressive symptoms are often reported during the onset of antidepressant treatment (Zienowicz et al. 2006; Cusin et al. 2007; Beasley et al. 1993; Jick et al. 2004). It is possible that the rapid rise in extracellular 5-HT contributes to the exacerbation of clinical symptoms during the onset of pharmacotherapy, whereas consequences of a long-term elevation of 5-HT, such as down-regulation of post-synaptic receptors or increases in neuronal plasticity-related gene expression (Duman 2004; Duman et al. 1997), contributes to the therapeutic effects of chronic antidepressant treatment. Consistent with this idea are reports that acute increases in 5-HT are associated with anxiogenic effects (Lowry et al. 2005; Graeff et al. 1993).

In addition to 5-HT, convincing evidence points to a role for noradrenergic neurons of the LC in mediating learned helplessness behaviors. Jay Weiss and colleagues have suggested that the behavioral consequences of uncontrollable stressors are produced by hyperactivation of LC noradrenergic neurons (Weiss and Simson 1985, 1986).

The role of LC hyperactivation is supported by several observations. First, uncontrollable stressors strongly activate catecholaminergic neurons in the LC as indicated by c-Fos labeling in tyrosine hydroxylase-positive neurons in the LC (Takase et al. 2005; Greenwood et al. 2003b). In fact, uncontrollable stressors activate the LC to the point of tissue norepinephrine (NE) depletion (Weiss et al. 1981). Second, ventricular infusion of a beta-adrenergic receptor agonist or intra-LC administration of an alpha2-adrenergic receptor antagonist, which disinhibits the LC, produces behaviors resembling those produced by uncontrollable stress (Weiss and Simson 1985). Third, intra-LC administration of an alpha2-adrenergic receptor agonist, which inhibits noradrenergic activity in the LC, reverses the behavioral consequences of uncontrollable stress (Simson et al. 1986). These data suggest that hyperactivation of the LC produces behaviors that resemble learned helplessness. Although release of galanin from LC nerve terminals into the ventral tegmental area (VTA) has been proposed as a mechanism for how LC hyperactivity leads to depressive symptoms (Weiss et al. 1998, 2005), given that hyperactivation of DRN 5-HT neurons is both necessary and sufficient to produce learned helplessness, it seems reasonable to suggest that LC NE could be contributing to learned helplessness by modulating the DRN. Indeed, the LC is an important source of NE in the DRN (Peyron et al. 1996), alpha1b adrenergic receptors are highly expressed on 5-HT neurons in the DRN (Day et al. 2004), and NE stimulates 5-HT neurons in the DRN (Trulson and Crisp 1984; Aghajanian 1985). Moreover, blockade of alpha1-adrenergic receptors in the DRN with intra-DRN administration of benoxathian during exposure to uncontrollable stress, but not during behavioral testing, prevents learned helplessness (Grahn et al. 2002). It is not surprising that an interaction between NE and 5-HT contributes to learned helplessness given the important roles of both monoamines in stress-related mood disorders. In fact, recent evidence suggests that LC neurons are hyperactive in depression (Zhu et al. 1999; Weiss et al. 1996; Gold and Chrousos et al. 1999), and Weiss and colleagues have pointed out that chronic treatment with virtually all effective antidepressant drugs decrease activity of LC NE neurons (Weiss et al. 2005; Grant and Weiss 2001). The roles of the DRN and LC in learned helplessness are summarized in Fig. 4 (left).

Given the important role of 5-HT hyperactivation in learned helplessness it is reasonable to predict that behavioral manipulations that effectively prevent learned helplessness behaviors would do so by preventing hyperactivation and sensitization of the DRN. One behavioral manipulation that prevents learned helplessness is prior exposure to controllable stress (Williams and Maier 1977; Amat et al. 2006), a phenomenon labeled behavioral immunization (Amat et al. 2006). Recent data indicate that the behavioral immunization effect of prior controllable stress is dependent upon activation of the ventral-medial prefrontal cortex (mPFCv), either during the original experience of controllable stress or the later experience of uncontrollable stress (Amat et al. 2006). Importantly, activation of mPFCv during controllable stress seems to produce behavioral immunization by inhibiting 5-HT neurons in the DRN during later exposure to uncontrollable shocks (Amat et al. 2005, 2006). Exercise is another behavioral manipulation that can prevent learned helplessness. The following section will describe converging data suggesting that exercise prevents learned helplessness by specifically constraining DRN 5-HT and LC NE activity during uncontrollable stressors.

Exercise Produces a Stress-Resistant Brain

When considering how exercise protects against learned helplessness, it is important to note that exercise does not globally modulate the entire physiological response to severe uncontrollable stressors. Although wheel running can blunt hypothalamic–pituitary–adrenal axis (HPA) responses to very mild stressors (Day et al. 2006; Droste et al. 2003, 2006, 2007) and can speed habituation of the HPA axis to repeated audiogenic stressor exposure (Sasse et al. in press), wheel running does not reliably affect the initial HPA response to more intense stressors, with both similar (Fleshner 2000; Dishman et al. 1997a, b) and augmented (Droste et al. 2003, 2007) HPA responses to forced swim, restraint, or uncontrollable foot shocks being reported in physically active, compared to sedentary, animals. Fleshner (2000) examined the effect of 6 weeks of wheel running on the corticosterone response to 100 uncontrollable tail shocks, the same tail shock procedure that produces learned helplessness in sedentary rats. Sedentary and wheel-run rats had identical increases in circulating corticosterone both immediately following the tail shock procedure and 24 h later, the time at which behavioral testing occurs. Additionally, c-Fos mapping studies indicate many stress-responsive brain regions that are activated to the same extent following uncontrollable tail shock stress in sedentary and wheel-run animals, including the basolateral and central nucleus of the amygdala (Greenwood et al. 2005a) and tyrosine hydroxylase-positive neurons in the caudal ventrolateral medulla (Greenwood et al. 2003b). It seems likely; therefore, that wheel running produces adaptations in specific neural circuits that are involved in mediating particular aspects of the stress response. Neurotrophic factors, serotonergic neurotransmission, and noradrenergic neurotransmission are among the factors that are implicated in stress-related

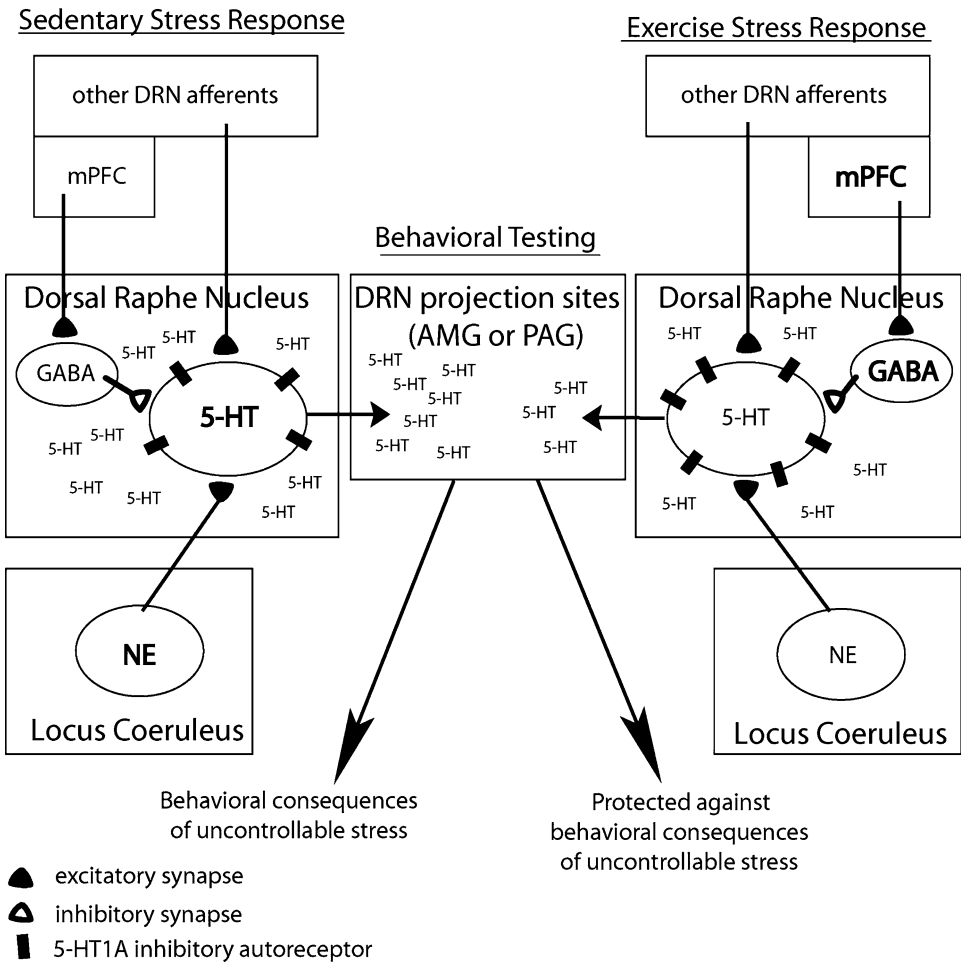

Fig. 4 Hyperactivation and sensitization of serotonin (5-HT) neurons in the dorsal raphe nucleus (DRN) is both necessary and sufficient for learned helplessness behaviors in sedentary animals. Uncontrollable stressors activate DRN afferents, including the locus coeruleus (LC); that could contribute to hyperactivation of 5-HT neurons in the DRN. Exaggerated 5-HT release in the DRN sensitizes DRN 5-HT neurons for a period of time, potentially by internalizing 5-HT1A autoreceptors. The sensitized DRN then responds to minor stressors; such as those experienced during behavioral testing, with enhanced release of 5-HT in DRN projection sites involved in expression of learned helplessness behaviors such as the amygdala (AMG) and periaqueductal gray (PAG). Exercise-induced plasticity could take place in many sites shown in this circuit to alter behavior. Wheel running increases 5-HT1A mRNA in the DRN and constrains stress-induced activation of norepinephrine (NE) neurons in the LC. Either of these effects of exercise could help constrain activation of DRN 5-HT neurons during exposure to uncontrollable stressors. Additionally, the medial prefrontal cortex (mPFC) is important for the protective effect of other behavioral manipulations, such as controllability, against learned helplessness behaviors. Increased mPFC-mediated inhibition of DRN 5-HT neurons could also contribute to the stress-buffering effects of physical activity. Relative activation of brain regions between sedentary and physically active animals is indicated by varying font size of brain regions. Larger font indicates a brain region that is highly activated during stressor exposure

mood disorders, including learned helplessness, and show responses to stress that are consistently altered by prior voluntary wheel running. The following section will describe the evidence that suggests these factors contribute mechanistically to effects of exercise on stress-evoked mood dysregulation.

Brain-Derived Neurotrophic Factor

Brain-derived neurotrophic factor (BDNF) is the most abundant neurotrophin in the brain and is critically involved in maintenance of neuronal health and plasticity (Barde 1994; Lo 1995). Voluntary exercise increases levels of BDNF in the hippocampus (Neeper et al. 1995, 1996), an effect that likely contributes to the beneficial effects of exercise on cognitive function (Kramer et al. 2005, 2006; Hillman et al. 2003, 2004, 2006) and learning and memory (Van der Borght et al. 2007; van Praag et al. 1999; Cotman and Egesser-Cesar 2002; Vaynman et al. 2004). It has recently been suggested that the increase in BDNF in the hippocampus of physically active rats also contributes to the antidepressant effects of physical activity (Duman

2005). This suggestion is based on the mounting evidence that reductions in hippocampal BDNF are associated with depressive symptoms and that therapeutic effects of antidepressant drugs are mediated through elevations in BDNF (for reviews, see Duman 2004; Duman et al. 1997; Duman and Monteggia 2006).

Although the role of BDNF in the protective effects of exercise in other animal models of stress-related mood disorders remains to be directly tested, hippocampal BDNF does not seem to be involved in learned helplessness nor in the mechanisms by which wheel running prevents learned helplessness. Stressor exposure reduces hippocampal BDNF (Smith et al. 1995) and wheel running prevents stress-induced decreases in BDNF (Greenwood et al. 2007a; Adlard and Cotman 2004), however, BDNF is not sensitive to stressor controllability. Both controllable and yoked uncontrollable shocks decrease hippocampal BDNF mRNA (Bland et al. 2007). Furthermore, although injections of BDNF into the dentate gyrus or CA3 region of the hippocampus can reverse escape learning deficits in sedentary rats previously exposed to uncontrollable foot shocks (Shirayama et al. 2002), injections of BDNF into the dentate gyrus do not prevent learned helplessness behaviors produced by uncontrollable tail shock administered in an environment distinct from that in which behavioral testing occurs (Greenwood et al. 2007a). Thus, while BDNF reductions may indeed contribute to the long-lasting shuttle box escape deficit produced by uncontrollable stress in an environment similar to that in which escape learning takes place, it is unlikely that hippocampal BDNF reductions contribute to learned helplessness as defined above. Not only is BDNF not likely to be involved in learned helplessness in sedentary rats, exercised rats with experimentally reduced levels of hippocampal BDNF are still protected against learned helplessness (Greenwood et al. 2007a). These data do not exclude a role of BDNF in antidepressant effects, or in other beneficial or therapeutic effects of exercise. Nonetheless, our results illuminate the importance of considering the roles of factors other than hippocampal BDNF in the protective effects of exercise against the development of learned helplessness.

Dorsal Raphe Serotonergic Neurons

Serotonergic systems are clearly involved in motor activity (Jacobs 1991; Jacobs and Fornal 1997; Bequet et al. 2001; Gomez-Merino et al. 2001). Elevated central 5-HT release during exhaustive exercise could contribute to the onset of fatigue (Blomstrand et al. 1989; Bailey et al. 1992, 1993) and has been suggested to play a role in centrally generated fatigue during exercise (Davis and Bailey 1997). The anatomy of the DRN, in particular, places it in a unique position to modulate both motor activity and stress-related behaviors. For example, the DRN projects to basal ganglia structures involved in motor control as well as limbic structures involved in depression and anxiety. In fact, a population of DRN 5-HT neurons has divergent axonal projections to both the caudate putamen and the amygdala (Imai et al. 1986), areas involved in motor control and fear/anxiety, respectively.

Both 5-HT and NE have long been implicated in the protective effects of exercise against stress-related mood disorders (Morgan 1985; Dunn and Dishman 1991; Dishman 1997). Recent work using voluntary wheel running suggests that physical activity constrains 5-HT responses to stressors, especially uncontrollable stressors. For example, 12 weeks of wheel running attenuates uncontrollable foot shock-induced elevations in the 5-HT metabolite, 5-hydroxyindole acetic acid, in the hippocampus and the amygdala (Dishman et al. 1997a); data consistent with decreased 5-HT neural activity and attenuated 5-HT release during stressor exposure. Additionally, compared to sedentary rats, rats allowed prior access to running wheels for 6 weeks have reduced c-Fos induction in 5-HT immunoreactive neurons in the rostral–mid DRN in response to uncontrollable tail shocks (Greenwood et al. 2003a). Importantly, both the reduction in stress-induced c-Fos in DRN 5-HT neurons and the protective effect of wheel running against learned helplessness behaviors follow the same time course. Neither the reduction in stress-induced 5-HT neural activity nor protection against learned helplessness occur in physically active animals after 3 weeks, but both occur after 6 weeks, of wheel running (Greenwood et al. 2005a). Because hyperactivation of 5-HT neurons in the DRN is necessary and sufficient to produce learned helplessness behaviors, constraint of 5-HT activity during stress could be an important factor contributing to the protective effect of exercise against learned helplessness. Constraint over central 5-HT responses to stress is an adaptation of exercise that is also consistent with the fatigue-delaying effects of wheel running during treadmill running to exhaustion (Davis and Bailey 1997; Campisi et al. 2003). In fact, rats bred for longer endurance times to exhaustion have elevated 5-HT1B terminal autoreceptor mRNA levels in the DRN compared to their exhaustion-prone counterparts (Foley et al. 2006). Since 5-HT1B autoreceptors are located on 5-HT axon terminals in DRN projections sites and function to inhibit 5-HT release (Adell et al. 2001), elevated 5-HT1B mRNA in the DRN is consistent with genetically selected constraint of 5-HT release in DRN terminal sites during exhaustive exercise.

There are many potential sites in which neural plasticity could take place that could account for constraint over stress-induced 5-HT activity in exercised animals (summarized in Fig. 4, right). One site of plasticity is, of course, the DRN itself. A consistent change that occurs in the DRN

following voluntary wheel running is an increase in levels of mRNA encoding for the 5-HT1A inhibitory autoreceptor (Greenwood et al. 2003b, 2005b). The increase in 5-HT1A mRNA occurs in a time-course consistent with the protective effect of wheel running against learned helplessness, that is, 6 weeks, but not 3 weeks, of wheel running increases levels of 5-HT1A mRNA in the DRN (Greenwood et al. 2005b). Increased levels of 5-HT1A autoreceptors could help constrain increases in 5-HT neural activity during stressor exposure because 5-HT1A autoreceptors have an inhibitory influence over DRN 5-HT neurons. Additionally, exercised rats with higher levels of 5-HT1A autoreceptors prior to stress could be resistant to stress-induced internalization of the 5-HT1A receptor, thus preventing sensitization of the DRN.

In addition to plasticity within the DRN, exercise could produce adaptations in afferent structures of the DRN which modulate activity of DRN 5-HT neurons. Although there are many such structures, some of which we have previously discussed (Greenwood et al. 2005a), the LC and the mPFCv require particular attention due to their established roles in learned helplessness.

Intense activation of the LC that occurs during uncontrollable stress could play a role in the development of learned helplessness by contributing to hyperactivation of 5-HT neurons in the DRN (Fig. 4, left). There is evidence that physical activity prevents hyperactivation and sensitization of the DRN by reducing the excitatory drive from the LC to the DRN. Rod K. Dishman and colleagues have accumulated evidence that wheel running attenuates stress-induced activation of NE neurons in the LC. In contrast to sedentary rats that demonstrate a depletion of LC NE content following uncontrollable foot shock, indicative of intense NE neural activity in the LC, 12 weeks of wheel running prevents uncontrollable foot shock-induced NE depletion in the LC (Dishman et al. 1997a). Wheel running was also reported to reduce NE release in the frontal cortex during foot shock (Soares et al. 1999). Using c-Fos as a marker of neural activation, we reported that 6 weeks of wheel running also attenuates uncontrollable tail-shock induced activation of tyrosine hydroxylase immunoreactive neurons in the LC (Greenwood et al. 2003b). Together, these data suggest that exercise constrains activation of NE neurons in the LC during uncontrollable stressors. It is possible that the constraint over LC drive during stress also contributes to constraining DRN drive. Indeed, the LC is the primary source of NE to the DRN (Peyron et al. 1996). In fact, the LC targets specifically the rostral–mid DRN, precisely the location in the DRN where the greatest attenuating effect of wheel running on stress-induced c-Fos induction is observed (Greenwood et al. 2003a). Supporting this idea is the observation that wheel running also prevents foot shock-induced depletion of NE in the DRN (Dishman et al. 1997a), suggesting that habitual wheel running constrains stress-induced activation of NE neurons that innervate the DRN. The mechanism(s) for wheel running-induced constraint of LC NE responses during stress is currently unknown. Wheel running does not alter mRNA (Soares et al. 1999) or protein (Greenwood et al. 2003b) levels of tyrosine hydroxylase in the LC, but does increase NE content in brainstem sections containing the LC (Dunn and Dishman 1991; Dunn et al. 1996; Dishman et al. 1997b). It is possible that, similar to the mechanism proposed in the DRN, facilitated alpha2A-adrenergic autoreceptor-mediated inhibition of LC NE neurons accounts for the constrained NE response during stress. Alpha2A-adrenergic receptors are presynaptic autoreceptors on NE neurons in the LC and function to inhibit activity of LC NE neurons similar to the mechanism proposed for the 5-HT1A autoreceptor in the DRN (Simson and Weiss 1987; Kimura and Nakamura 1987). Although this is a possibility, the last bit of data in the current review shows that levels of alpha2A-adrenergic receptor mRNA in the LC of sedentary and physically active rats is similar (Fig. 5). Thus, if facilitated alpha2A-adrenergic receptor-mediated auto-inhibition of the LC is indeed involved in the mechanisms by which exercise constrains LC NE drive to the DRN during stress, then the plasticity in the alpha2A-adrenergic receptor must occur post-transcription.

Two possibilities for how wheel running constrains activation of DRN 5-HT neurons during stress, enhanced 5-HT1A-mediated auto-inhibition of DRN 5-HT neurons and constraint of LC–DRN drive, have so far been discussed. A third intriguing possibility involves the mPFC.

Growing evidence points to a role for the mPFC in general stress resistance (Tavares and Correa 2006; Figueiredo et al. 2003; Rangel et al. 2003; Jinks and McGregor 1997; Gerrits et al. 2003; Maier et al. 2006) and, therefore, damage to the mPFC could be involved in stress-related mood disorders (Drevets 2000). Indeed, exposure to chronic stress impairs cytogenesis in the mPFC and chronic treatment with antidepressants reverse this effect (Czeh et al. 2006). Reduced volume (Taki et al. 2005) and decreased number and size of neurons and glial cells (Rajkowska 2000, 2002) have been observed in the PFC of deceased depressed patients relative to controls. Finally, neuroimaging studies indicate that depressed patients and patients with post-traumatic stress disorder have disturbed cerebral blood flow and metabolic activity in the mPFC (Baker et al. 1997; Bremmer et al. 1999). Antidepressant treatment can reverse these deficits (Kennedy et al. 2001).

A role for the mPFC in resistance to learned helplessness has recently been elucidated. The infralimbic (IL) region of the mPFCv provides the major cortical input to the DRN, although the prelimbic (PL) region provides

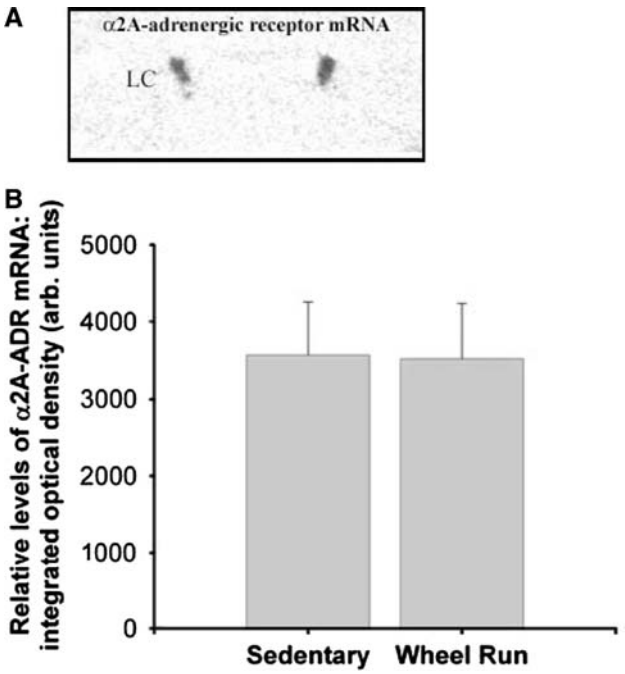

Fig. 5 Expression of alpha2A-adrenergic receptor mRNA in the locus coeruleus (LC) of sedentary and physically active rats. Adult, male Fischer 344 rats ($n = 7$/group) either remained sedentary or were allowed voluntary access to running wheels for 6 weeks. Between 8:00 and 10:00 a.m. rats were rapidly killed by decapitation, brains were removed and processed with in situ hybridization histochemistry for the alpha2A-adrenergic receptor mRNA (690 base pairs, courtesy of Serge Campeau, University of Colorado, Boulder) following previously published protocols (Greenwood et al. 2005b). (**a**) Autoradiograph showing alpha2A-adrenergic receptor mRNA in the LC of a sedentary rat. (**b**) Relative levels of alpha2A-adrenergic receptor mRNA in sedentary and physically active rats. ANOVA revealed that 6 weeks of wheel running did not alter levels of alpha2A-adrenergic receptor mRNA ($F(1, 12) = .003$; $P > .05$)

DRN afferents as well (Peyron et al. 1998; Vertes 2004). Glutamate neurons in these regions (Lee et al. 2003) project to and synapse on predominantly GABAergic neurons in the DRN and thus inhibit the activity of 5-HT neurons (Varga et al. 2001). Indeed, electrical stimulation of the IL inhibits activity of DRN 5-HT neurons (Hajos et al. 1998). Behavioral studies indicate that this circuit is important for resistance against stress-induced activation of DRN 5-HT neurons and subsequent behavioral consequences of uncontrollable stress. Specifically, temporarily inhibiting the mPFC (both the ventral PL and IL) with intra-mPFC injections of the GABAA agonist muscimol during exposure to controllable tail shock activates 5-HT neurons in the DRN to an extent equal to that produced by uncontrollable stress. Moreover, rats exposed to controllable stress during mPFC inactivation display behaviors typically produced only after uncontrollable stress; namely exaggerated fear and escape deficits, 24 h later (Amat et al. 2005). These data indicate that activation of the mPFC is necessary for the previously discussed behavioral immunization effect of controllability.

Given the clear role of the mPFC in the protective effect of controllability, it is appealing to hypothesize that perhaps exercise also increases mPFC-mediated inhibition of DRN 5-HT neurons, thus preventing the development of learned helplessness. Very little work has yet addressed the effects of physical activity on specifically the mPFC. Exercise does, however, increase the volume of the PFC in humans (Colcombe et al. 2006) and wheel running increases learning and memory (Vaynman et al. 2004; Gomez-Pinilla et al. 1998). The data on the effect of exercise on mPFC activation are mixed; some studies report an increase in oxygen utilization during exercise (Ide et al. 1999; Suzuki et al. 2002) while others report a decrease (Dietrich 2006). Regardless of this discrepancy, exercise does increase executive control functions involving the PFC (Hillman et al. 2003, 2004, 2005, 2006; Harada et al. 2004; Kramer et al. 1999, 2002; Dishman et al. 2006). Whether the mPFC is involved in the protective effect of exercise against learned helplessness and stress-related mood disorders, in general, remains unknown.

This review elucidates potential neural mechanisms for exercise-induced stress resistance. Clearly, exercise stimulates adaptations in several neural circuits and brain regions that are both stress sensitive and involved in learned helplessness. We speculate that the impact exercise has on the brain is not specific to these brain areas. Rather it is plausible that exercise elevates the brain's capacity for plasticity, perhaps in part due to increases in growth factors. The neural circuitry most impacted by the elevation in plasticity may be those areas that are responding to environmental demands and/or generating behavioral responses to those demands.

Summary

Exercise is an accessible, inexpensive, behavioral manipulation that acts both therapeutically to alleviate symptoms of stress-related mood disorders, and prophylactically to reduce the occurrence of stress-related mood disorders. Learned helplessness is a useful animal model of stress-related mood disorders that can be prevented by wheel running. When studying the effects of exercise or other manipulations on behavioral consequences of uncontrollable stress or learned helplessness, however, researchers should be conscious of the contextual relationship between the stressor and the testing environments. The time course of the behavioral consequences of uncontrollable stress, the mechanisms involved, and the effects of exercise all vary depending on this relationship. Learned helplessness behaviors are specifically those behavioral consequences of

uncontrollable, but not controllable, stress that are present in an environment that is very different from the original stressor environment.

Hyperactivation of 5-HT neurons in the DRN is both necessary and sufficient to produce learned helplessness behaviors. Uncontrollable shocks hyperactivate the DRN, potentially via intense LC–DRN drive. Hyperactivation of the DRN leads to sensitization of the DRN, exaggerated 5-HT release in DRN projection sites during behavioral testing, and the expression of learned helplessness. It is proposed here that 6 weeks of wheel running prevents learned helplessness and constrains activation of DRN 5-HT neurons during uncontrollable stress by (1) enhanced 5-HT1A-mediated auto-inhibition of 5-HT neurons, (2) blunted LC–DRN drive, and/or (3) facilitated mPFC-mediated inhibition of DRN 5-HT neurons. Identifying the mechanisms by which wheel running prevents learned helplessness could shed light on the complex neurobiology of depression and anxiety, potentially leading to novel strategies for the prevention of stress-related mood disorders.

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