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Animal Models of Resistance Exercise and their Application to Neuroscience Research

Justin C. Strickland[a] and **Mark A. Smith**[b,c,*]

[a]Department of Psychology, University of Kentucky, Lexington, KY, USA

[b]Department of Psychology, Davidson College, Davidson, NC, USA

[c]Program in Neuroscience, Davidson College, Davidson, NC, USA

Abstract

Background—Numerous studies have demonstrated that participation in regular resistance exercise (e.g., strength training) is associated with improvements in mental health, memory, and cognition. However, less is known about the neurobiological mechanisms mediating these effects. The goal of this mini-review is to describe and evaluate the available animal models of resistance exercise that may prove useful for examining CNS activity.

New Method—Various models have been developed to examine resistance exercise in laboratory animals.

Comparison with Existing Methods—Resistance exercise models vary in how the resistance manipulation is applied, either through direct stimulation of the muscle (e.g., in situ models) or through behavior maintained by operant contingencies (e.g., whole organism models). Each model presents distinct advantages and disadvantages for examining central nervous system (CNS) activity, and consideration of these attributes is essential for the future investigation of underlying neurobiological substrates.

Results—Potential neurobiological mechanisms mediating the effects of resistance exercise on pain, anxiety, memory, and drug use have been efficiently and effectively investigated using resistance exercise models that minimize stress and maximize the relative contribution of resistance over aerobic factors.

Conclusions—Whole organism resistance exercise models that (1) limit the use of potentially stressful stimuli and (2) minimize the contribution of aerobic factors will be critical for examining resistance exercise and CNS function.

Keywords

cognition; mental health; neurobiology; resistance training; rodent; strength training

[*]Corresponding Author: Mark A. Smith, Ph.D., Department of Psychology, Box 7037, Davidson College, Davidson, NC 28035-7037, Phone: 704-894-2470, Fax: 704-894-2512, masmith@davidson.edu.

1. Introduction

Epidemiological studies have consistently reported positive effects of physical activity on measures of mental health, including reductions in depression (Mammen and Faulkner, 2013) and anxiety (DeBoer et al., 2012), as well as increases in cognition and quality of life (Penedo and Dahn, 2005; Windle et al., 2010). Studies in the animal and human laboratory examining aerobic exercise (e.g., running, swimming) have identified numerous neurobiological mechanisms that might mediate these effects. These studies have shown that aerobic exercise alters neurotransmitters, trophic factors, and neuroanatomical structures that contribute to the effects of aerobic exercise on psychological well-being (Dishman et al., 2006). In contrast to the extensive literature devoted to the neurobiological effects of aerobic exercise, less research exists evaluating the neurobiological effects of resistance exercise (i.e., strength training). Given that resistance exercise also confers cognitive and mental health benefits in humans (see review by O'Connor et al., 2010), it is critical that animal models be developed and evaluated for examining underlying neurobiological systems.

Recent reviews have evaluated the use of and potential applications for resistance exercise models utilized in the animal laboratory. These reviews have described the development of rodent models for studying aerobic and resistance exercise physiology (Seo et al., 2014), the translational relevance of exercise models for understanding brain plasticity (Voss et al., 2013), and the use of resistance models for studying skeletal muscle hypertrophy (Cholewa et al., 2014). The primary objective of this mini-review is to evaluate the available animal models for examining the effects of resistance exercise on CNS activity. To this end, we describe and highlight the relative advantages and disadvantages of the available preclinical models for studying resistance exercise and neurobiological effects. We also identify areas where significant advances have been made in understanding the neuroscience of resistance exercise by using these models, such as the neurobiological effects of resistance exercise as they relate to pain, anxiety, memory and cognition, and drug use. Ultimately, attention to key design features, namely the minimization of stressful stimuli and aerobic factors, will be important for guiding future research on resistance exercise and CNS activity conducted in the animal laboratory.

2. Resistance Exercise in Human Populations

Resistance exercise is used by humans to increase muscle strength and size through resistance-induced muscular contraction (Physical Activity Guidelines Advisory Committee, 2008). Equipment such as free weights, elastic bands, or resistance machines may be used to evoke eccentric (i.e., lengthening) or concentric (i.e., shortening) muscle movements of single or multiple-joint action (American College of Sports Medicine, 2009). Resistance exercises are typically performed as a series of sets with multiple repetitions incorporating a variety of resistance types and muscles groups. Exercise output can be quantified as repetition maximums with 1RM as the maximal amount that can be lifted in a single repetition of a selected exercise. Resistance exercise is more prevalent in men than women, with 27% of males and 19% of females in the United States reporting routine resistance training (Schoenborn et al., 2013). Importantly, participation in regular resistance exercise is associated with decreases in anxiety and depression as well as increases in cognition and

general quality of life (see reviews by O'Connor et al., 2010; Strickland and Smith, 2014). Although these improvements have been well documented, the neurobiological mechanisms mediating such effects have not. Identifying underlying neurobiological systems is critical for determining how resistance exercise contributes to psychological well-being and for hastening the design of therapeutic interventions that involve resistance training.

3. Animal Models of Resistance Exercise

Animal models provide one way to examine changes in CNS activity induced by resistance exercise. Importantly, animal models provide increased control over exercise parameters (e.g., frequency, load, duration), lifestyle behaviors (e.g., diet), and other factors that might influence CNS function. Our goal is not to provide an exhaustive review of all studies using specific models of resistance exercise (for reviews focusing on muscle physiology, see Alway et al., 2005; Cholewa et al., 2014; Lowe and Alway, 2002). Rather, our purpose is to describe and evaluate the available models of resistance exercise that may prove useful for examining CNS activity by providing case examples and critical evaluation of advantages and disadvantages.

Animal models of resistance training generally fall into two categories. First, in situ models are those in which the resistance manipulation is applied directly to the muscle of interest, such as through electrical stimulation, and often involve an anesthetized subject. In contrast, whole organism models are performed by a conscious organism and typically involve behavior maintained by operant contingencies. Rodents are the most popular model organism used in resistance exercise studies due to the availability of genetic manipulations (e.g., knockouts), the ease of anatomical evaluation post exercise, and their mammalian phylogeny. Consequently, we have chosen to focus on rodent-based models for this mini-review.

3.1 In Situ Models

In situ models involve the direct stimulation of muscle and include electrical-stimulation, chronic-stretch, and compensatory overload models (Table 1). Although these models focus on peripheral tissue, in situ procedures will be important for understanding the neurobiological effects of resistance exercise by providing insight into peripheral-to-central signaling mechanisms activated during muscle hypertrophy. One of the most popular in situ models is electrical stimulation, wherein an electrical current is applied to the muscle to evoke involuntary concentric or eccentric muscle contraction. For example, in one of the first studies modeling resistance exercise using electrical stimulation, a subcutaneous electrode was placed on the plantar flexor of an anesthetized rat and stimulated with 15 V electrical pulses to lift attached weights (Wong and Booth, 1988). Following 16 weeks of training (24 repetitions every 3 days) an increase in gastrocnemius (GAS) wet weight and protein content was observed, thereby supporting the validity of the model. Electrical stimulation is particularly useful in studying hypertrophic cell-signaling pathways due to the specific and maximal activation of the muscles of interest (see review by Hortobagyi and Maffiuletti, 2011). Nevertheless, electrical stimulation models may be limited when examining changes in CNS activity given the required and repeated administration of anesthesia and application

of potentially stressful stimuli (i.e., electrical shock) that may affect CNS activity independent of muscle hypertrophy.

Another widely used in situ model is chronic stretch. This model makes use of the observation that a muscle kept in a shortened position for long durations will atrophy, whereas a muscle cast in a lengthened position will maintain and often increase muscle fiber hypertrophy, length, and contractile performance. In chronic stretch, the hindlimb is immobilized in a lengthened position using a fiberglass cast resulting in extensor digitorum longus muscle growth and protein synthesis after 7 days of immobilization (Goldspink, 1977). Chronic stretch provides an excellent internal control because the opposite leg can serve as a comparison for an individual subject's natural muscle growth. This strength has been particularly important for elucidating the hypertrophic outcomes of resistance exercise (e.g., Goldspink et al., 1995; Goldspink, 2005), and may also be important for understanding peripheral-to-central signaling mechanisms invoked by muscle hypertrophy. However, chronic stretch is also criticized as a resistance exercise model because it provides constant resistance application rather than the intermittent application typical of human training.

Compensatory overload is another in situ model in which the synergists (i.e., muscles that work together with another muscle to make movement) of a skeletal muscle are removed in order to overload the contractile response of the remaining muscle during future movement (Goldberg, 1967; Roy et al., 1982). Compensatory overload provides a rapid assessment of muscle growth due to the robust hypertrophy observed in remaining muscle in the days following surgery. These procedures may be particularly advantageous for understanding the effects of resistance exercise during critical periods of development that are brief in duration and like other in situ models may reveal important peripheral-to-central signaling mechanisms activated during muscle hypertrophy. However, compensatory overload also results in an inflammatory response that develops in conjunction with muscle hypertrophy (Armstrong et al., 1979). These immunological responses may mask the direct effects of resistance exercise on CNS function, which limits the appeal of compensatory overload models for understanding central effects.

3.2 Whole Organism Models

Whole organism models are performed in conscious subjects and typically involve volitional behavior maintained by either positive or negative reinforcement. Behavior is maintained in positive reinforcement procedures through the application of an appetitive stimulus (e.g., food). Behavior is maintained in negative reinforcement procedures through escape or avoidance of an aversive stimulus (e.g., electric shock). It is possible that positive and negative reinforcement contingencies may produce different or even opposing effects on underlying neurobiological systems; however, the relationship between reinforcement contingencies and the neurobiological effects of resistance exercise has not been systematically examined. Several whole organism models have been developed, including those using ladder climbing, resistance wheel running, squat-based exercises, and water-based exercises (Table 1).

Ladder climbing is one of the most popular models of resistance exercise. Most procedures using ladder climbing begin with a subject positioned at the bottom of a vertical ladder (80

to 90° incline; ~ 50 to 100 cm high) with variable loads attached to the tail (Duncan et al., 1998; Hornberger and Farrar, 2004; Yarasheski et al., 1990). The dynamic movement upwards is typically maintained by shock avoidance (Hornberger and Farrar, 2004; Silveira et al., 2011), but food reinforcement has also been used (Yarasheski et al., 1990). Training load is manipulated via the weight affixed to the tail. As an alternative to these ladder climb methods, water bottles can be affixed to the top of a ladder in the home cage as a means to establish regular climbing in the subject's home environment but in the absence of any additional load (Kang et al., 2002). This procedure limits the stress produced by electronic shock, but it does not control for exercise output, and without the use of telemetric devices it is unable to determine individual differences in climbing behavior.

Whereas many ladder-climbing procedures use noxious stimuli (e.g., electric shock, food deprivation) to maintain behavior, others have successfully maintained climbing without the repeated use of potentially painful stimuli (Cassilhas et al., 2012a, 2012b, 2013; Nokia et al., 2016; Strickland et al., 2016). For example, our laboratory recently used a modified climbing protocol in which rats were trained to climb a ladder (46 cm long, 90° incline) with a dark chamber at the top and a bright light positioned at the bottom of the ladder to motivate subjects to climb (Strickland et al., 2016). In this study, sessions were conducted 6 days per week with 3 sets performed at increasing loads attached to a weighted harness: 8 climbs at 70% BW, 6 climbs at 85% BW, and 4 climbs at 100% BW. Following 6 weeks of resistance training, we observed increases in both hindlimb grip strength and GAS mass. The use of increasing weight with decreasing sets (i.e., pyramid loading) is modeled after the popular training methods used by human athletes and is similar to resistance methods used in human laboratory studies (e.g., Charro et al., 2010). Furthermore, the weighted harness is a vest that fits over the shoulders to model weight-bearing exercises used by humans, and it avoids the discomfort of weighted loads placed on the tail. Ladder climbing thus appears to provide a face and construct valid (i.e., relevant muscle changes) model of resistance exercise. Importantly, ladder models have shown relative utility in studying CNS activity by regulating exercise output and limiting pain, stress, and aerobic involvement (as described in Section 4). However, the relative specificity of exercise to hindlimb activity must be noted when considering the use of ladder-climbing models exclusively.

Resistance wheel running is another popular model for resistance exercise. Here, a weighted load is added to a traditional laboratory running wheel in order to increase the work necessary to overcome the running wheel's inertia during locomotion (Ishihara et al., 1998). Additional reinforcement (e.g., food access) is not necessary to promote exercise in these studies suggesting that weighted wheel running is intrinsically rewarding (see Belke and Heyman, 1994; Iverson, 1998). In one of the first studies to employ progressive resistance running, additional loads were added to the running wheel for 8 weeks to reach a terminal weight load of 60% body weight (BW; Ishihara et al., 1998). Relative to subjects in no-load or sedentary control conditions, the loaded wheel runners showed an increase in plantaris mass. Interestingly, changes in muscle weight and cross-sectional area were correlated with average running distance and total work in the loaded running group, but not in the no-load group. Numerous studies have replicated these findings, with increases in muscle size observed in mice (e.g., Konhilas et al., 2005) and rats (e.g., Legerlotz et al., 2008) performing progressive resistance wheel running. Important to note is that patterns of wheel

running differ when animals are given access to loaded versus unloaded wheels; for example, one study found shorter, faster, and more frequent wheel running in resistance conditions despite no differences in the total distance traveled (Legerlotz et al., 2008). Given the differences in exercise topography, direct comparisons between loaded and unloaded conditions must be interpreted with caution. Resistance wheel running procedures are appealing from the standpoint that exercise is voluntary (see Aparicio et al., 2011 for an example of forced treadmill procedures), and variability in exercise output can be used to correlate behavior with neurobiological changes. This strength may be particularly important when determining the optimal loading parameters for functional changes following resistance exercise. The combination of aerobic and resistance modalities in weighted running models may also prove translationally relevant given the high proportion of training procedures in humans that mix aerobic and resistance exercise (e.g., cross and circuit training). However, care must be taken in these types of procedures to isolate the relative contributions of aerobic versus resistance factors. Fortunately, several methods are available to measure metabolic expenditure during physical activity in laboratory rodents (see review by Speakman, 2013). For example, respiratory exchange ratios provide a measure of the ratio of carbon dioxide production (VCO_2) to oxygen consumption (VO_2) and have been effectively used in exercise studies to compare energy and substrate metabolism in rodents (Patch and Brooks, 1980; Rezende et al., 2006; Schefer and Talan, 1996). Measurements such as these should help to clarify the independent and combined contributions of aerobic and resistance exercise to CNS activity.

Squat-based exercises are also commonly used as a whole animal model of resistance exercise (e.g., Barauna et al., 2005, 2007; Notomi et al., 2000; Tamaki et al., 1992). In these procedures, the subject wears a canvas jacket attached to a wooden arm loaded with variable weights. A brief electrical shock is applied via surface electrodes to the subject's tail resulting in a dynamic upward lifting of the loaded arm. Training loads in these studies are determined by setting the RM and training the subject at percentages of that RM (e.g., 65–75% RM in Tamaki et al., 1992). These conditions have produced increases in GAS and plantaris mass relative to sedentary controls that are not observed in animals trained using aerobic sprint exercises (Tamaki et al., 1992). Other squat-based procedures have trained subjects to press an illuminated bar placed at an elevated position while the subject wears a weighted harness (Fluckey et al., 1995). In these procedures, lever pressing typically postpones an electric shock, which is sufficient to maintain the lifting behavior throughout a session (Hernandez et al., 2000; Nilsson et al., 2010). Modified versions of these squat exercises replace the harness with a weighted neck-ring that is lifted via a nose poke (Wirth et al., 2003). With this procedure, subjects are kept food restricted and lever pressing results in a food reward, which is sufficient to maintain the squat behavior with repeated training. One advantage of squat-based models is that they closely mimic squat exercises commonly used in human populations and therefore have improved face validity. Furthermore, these models may better parallel the time course of hypertrophic outcomes observed in human training conditions given that muscle mass and strength gains only occur after long-term training (e.g., 6 to 8 weeks). The main limitation of squat-based procedures in the context of neurobiological research is the typical use of electrical shock to maintain behavior. Stress induced by these noxious stimuli can differentially alter CNS activity and function (e.g.,

Deak et al., 2013; Leuner and Gould, 2010), which may in turn confound interpretation of exercise-induced neurobiological effects.

Squat-based methods have also been adapted for use in conjunction with other experimental procedures. For example, in hindlimb suspension a subject's hindlimbs are tethered to the top of the home cage preventing regular locomotion and leading to muscle atrophy that is thought to model long-term muscle disuse (e.g., paralysis) (Morey-Holton et al., 2005). Resistance exercise is introduced in these models by using pulley systems in which subjects must press a bar at the front of the apparatus to avoid an electric shock (Fluckey et al., 2002). Various loads are applied to the flywheel to allow experimental manipulation of exercise output. Such research has been critical in the development of resistance training programs used to prevent muscle atrophy (Dupont-Versteegden et al., 2006; Fluckey et al., 2002, 2004). Flywheel methods provide a unique opportunity to model the effects of resistance exercise on CNS activity in populations where long-term muscle disuse is observed (e.g., paraplegics, those on medical bed rest). Although this flywheel method is not commonly used outside of hindlimb suspension studies, likely due to its limited generalizability to other participant populations, this research demonstrates the potential utility of combining resistance exercise procedures with other existing neuroscience methods.

Swimming and water-based exercises also provide a unique means to model resistance exercise. For example, a submersion procedure in which the subject is placed at the bottom of a shallow pool with a weighted harness is a common water-based resistance model (e.g., Cunha et al., 2005; de Souza et al., 2011; Haraguchi et al., 2011). In this model, the subject is submerged in water with progressively increasing loads attached to a weighted vest and must jump in order to escape the water. Muscle change in these studies is not as pronounced as other models; for example, 8 weeks of submersion exercise produced decreases in abdominal fat but also decreases in GAS and total mass (Haraguchi et al., 2011). In lieu of a submersion model, other researchers have used bouts of swimming where the subject is forced to swim with a low intensity weighted load (e.g., 12% BW) for short and repetitive bouts (Turchanowa et al., 2000). Water-based resistance training is frequently used in human populations, particularly for individuals for whom high impact resistance training is not possible (e.g., older populations; Katsura et al., 2010). Consequently, water models provide differentiation between the effects of water-based training versus traditional weight lifting procedures. However, the stressful nature of complete submersion may produce neurobiological changes that mask the effects of the resistance components. The development of water-based procedures that limit potentially stressful stimuli will be important in determining the specific role of water-based training methods.

4. Recent Advances in Resistance Exercise and CNS Activity

Although research on the central effects of resistance exercise is still in its infancy, recent years have seen a growth in the use of animal models to understand the neurotransmitters, neurotrophic factors, and neuroanatomical regions associated with resistance training. These findings have advanced our knowledge of the centrally mediated effects of resistance exercise in varied and distinct health domains, including pain, anxiety, cognition, and drug

use. This body of literature has also demonstrated a general concordance with the human literature regarding the behavioral effects of resistance exercise, including improvements in cognition and memory as well as decreases in pain and drug use. The experimental designs used in these studies suggest important design features, including the minimization of stress and aerobic factors, which will likely provide the most direct evidence for the relationship between resistance training and changes in CNS structure and function.

4.1 Nociception: Opioids, Adrenoreceptors, and Endocannabinoids

Several clinical trials have demonstrated decreases in chronic pain following participation in resistance training (e.g., Hayden et al., 2005). Similar results are observed in animal models, with several recent studies demonstrating the antinociceptive effects of resistance exercise (Table 2). These studies have shown that resistance exercise as modeled by squat-based methods increases nociceptive thresholds in tail-flick and paw-withdrawal procedures relative to sedentary controls (de Souza et al., 2013; Galdino et al., 2010, 2014a, 2014b). These antinociceptive effects are apparent immediately following an acute bout of exercise, but tend to diminish with repeated training (i.e., longer than 45 days; Galdino et al., 2010). Although the central mechanism of action remains undetermined, subcutaneous administration of the opioid antagonist naloxone reverses antinociceptive effects when administered immediately prior to exercise (Galdino et al., 2010). This finding suggests a role for endogenous opioids in exercise-induced antinociception; however, it remains unknown if this effect is peripherally or centrally mediated. Systemic injections of the adrenergic receptor antagonists, yohimbine, rauwolscine, and BRL 44408 also reverse the antinociceptive effects of resistance exercise, but fail to do so when administered via intracerebroventricular or intrathecal routes (de Souza et al., 2013). Consequently, the involvement of adrenergic signaling in exercise-induced antinociception is likely of peripheral rather than central origin. Galdino and colleagues (2014b) recently suggested a novel role for the endocannabinoid system in mediating resistance exercise's antinociceptive effects. In that study, systematic and central administration of CB_1 or CB_2 inverse agonists prevented exercise-induced antinociception, whereas administration of endocannabinoid reuptake or metabolizing enzyme inhibitors prolonged and enhanced exercise-induced antinociception. Histological analysis also indicated that exercise subjects showed increased expression and activation of CB_1 receptors in the dorsal and ventral periaqueductal region, further supporting the involvement of the endocannabinoid system.

A key limitation of these studies is the use of electric tail shock to motivate squat-based movements. Electric shock is known to induce antinociception in laboratory animals through the activation and involvement of the endogenous opioid system (Nabeshima et al., 1985). As a result, the findings relating exercise-induced antinociception to opioid signaling may be affected by the use of electric shock during resistance exercise; however, a recent study demonstrated antinociception in resistance trained subjects relative to sedentary controls that received electrical stimulation "yoked" to their resistance partners (Galdino et al., 2014b). Future studies that maintain behavior through the use of non-noxious stimuli will be needed to fully elucidate the mechanisms mediating exercise-induced antinociception.

4.2 Anxiety and the Hypothalamic-Pituitary-Adrenal Axis

Numerous studies have demonstrated the anxiolytic effects of resistance exercise following both acute sessions and long-term training in human subjects (see review by Strickland and Smith, 2014). Although no studies to date have examined the effects of resistance exercise on traditional models of anxiety (e.g., elevated plus maze), several studies have indicated a role in associative learning processes that may be functionally related to anxiety (e.g., avoidance or fear conditioning). In the first of these studies, subjects were trained for 8 weeks using a ladder-climbing procedure and then tested in a passive avoidance task (Cassilhas et al., 2012b). In this task, one compartment of a chamber was paired with electrical shock in a single session, and then the latency to enter the shock-associated compartment measured 24 hours later. Resistance training improved fear conditioning, almost doubling the latency for rats to enter the shock-associated compartment relative to sedentary controls. Similar effects were observed in a later study in which a combination of aerobic treadmill running and resistance ladder climbing increased fear conditioning relative to sedentary controls (Kim et al., 2016). The effects of an acute bout of resistance training (i.e., ladder climbing) immediately following contextual and auditory fear conditioning using electric shock was also recently examined (Fernandes et al., 2016). Resistance exercise enhanced contextual, but not auditory, fear conditioning as measured by a freezing response. However, the context test occurred 24 h after exercise, whereas the tone test occurred 48 h following; therefore, it is unclear if the distinction in conditioning was a function of differences in the stimulus or time. Taken together, these studies indicate that both acute and chronic resistance training improves fear conditioning that may be functionally related to anxiety and related behaviors.

A growing body of literature also indicates that resistance exercise influences the hypothalamic-pituitary-adrenal (HPA) axis, a neural system implicated in anxiety disorders. Anxiety disorders are often characterized as disorders of the HPA axis because unanticipated or extended stress responses along the HPA axis result in sympathetic dysregulation, fear, and hypervigilence (Chrousos, 2009). A rich body of literature has demonstrated modulation of cortisol activity (i.e., the functional output of the HPA axis) by resistance exercise in human populations (see reviews by Crewther et al., 2006, 2011). Specifically, resistance exercise produces acute increases in circulating cortisol with recovery to resting basal levels following exercise cessation (e.g., Ahtiainen et al., 2004; Hakkinen and Pakarinen, 1993). Similar transient increases in corticosterone (i.e., the rodent equivalent of cortisol) following resistance training have been observed in laboratory animals (Table 2; Aparicio et al., 2014; Ebal et al., 2007). These findings are important because glucocorticoids, such as corticosterone, regulate stress-induced HPA axis hormone secretion (see reviews by Dallman et al., 1987; Keller-Wood and Dallman, 1984). By producing a reliable, controllable, and predicable stress event, resistance exercise may encourage adaptive stress responses and feedback-driven regulation along the HPA axis (for a discussion of stress response predictability see Koolhaus et al., 2011). In this respect, resistance exercise may help to normalize HPA axis function in populations where disrupted signaling occurs and where stress responses are often unsignaled and unpredictable (e.g. individuals with anxiety disorders; Chrousos, 2009). Future studies will be necessary to test this regulation-feedback

hypothesis and the underlying neurobiological mechanisms relating resistance exercise and changes in anxiety.

Resistance exercise also regulates other hormonal outputs related to the HPA axis, namely oxytocin and vasopressin (Farina et al., 2014; Lipari et al., 2010). These studies have shown that ladder climbing produces a decrease in oxytocin-positive neurons in the paraventricular nucleus of the hypothalamus, indicative of either an increase in the release or decrease in the production of oxytocin in this region (Farina et al., 2014). Although resistance training does not produce immediate changes in vasopressin concentrations, increases in vasopressin-positive neurons are observed in the paraventricular nucleus following a 15-day rest period (Farina et al., 2014). These findings are important because oxytocin and vasopressin are putative therapeutic targets for a variety of mental health outcomes, including anxiety, autism, and substance use disorders (Matsuzaki et al., 2012; McGregor and Bowen, 2012; Stavropoulos and Carver, 2013). Future studies that include models of anxiety-like behavior in the context of these neurobiological changes will help clarify the role of HPA axis function in the anxiolytic effects of resistance exercise.

4.3 Cognition, Memory, and Neurotropic Factors

Resistance exercise in human populations is also associated with increases in cognitive performance and memory, particularly in older adults (e.g., Cassilhas et al., 2007; Ozkaya et al., 2005). Research in laboratory animals has examined these cognitive-enhancing effects and many of these studies have revealed functional changes in the hippocampus, a forebrain structure important for learning and memory (Table 2; Cassilhas et al., 2012a; Cassilhas et al., 2012b; Lee et al., 2012; Suijo et al., 2013; but see Nokia et al. 2016). For example, resistance wheel running increases hippocampal neurogenesis after 4 weeks of exercise (Lee et al., 2013). Ladder-climbing also increases hippocampal cell proliferation and anti-apoptotic protein expression over a comparable training period (Gomes et al., 2014, but see Nokia et al., 2016). Similarly, resistance exercise improves spatial memory, with access to a resistance running wheel (Lee et al., 2012; Suijo et al., 2013) or regular ladder climbing with weighted loads (Cassilhas et al., 2012a) decreasing the latency and/or distance to reach a platform in a Morris water maze task (for details on this task see Ang et al., 2006; Morris et al., 1982). As described in Section 4.2, resistance training also improves associative learning as measured by fear conditioning tests (Cassilhas et al., 2012b; Fernandes et al., 2016; Kim et al., 2016).

One potential neurobiological mechanism mediating the cognitive-enhancing effects of resistance exercise is brain-derived neurotrophic factor (BDNF). Numerous studies have demonstrated the regulatory effects of BDNF on memory and cognitive performance through its influence on hippocampal plasticity (Kuipers and Bramham, 2006; Vivar et al., 2013). When given access to a resistance exercise wheel for 4 weeks with a terminal resistance of 30% BW, increases in hippocampal BDNF mRNA expression, as well as the downstream effectors, TrkB, CREB, PKA, PKC, and MAPK, were observed in laboratory rats (Lee et al., 2012). Similar increases in hippocampal BDNF protein expression were reported after aerobic treadmill training (Cassilhas et al., 2012a) but not ladder-climb training (Gomes et al. 2014) unless ladder climbing was combined with treadmill running

(Kim et al., 2016). It is possible that these contrasting outcomes are due to the aerobic component present in several of these models of resistance training. Indeed, resistance wheel running produces changes in hippocampal neurogenesis in a comparable manner to load-free running, indicating significant overlap in their consequent effects (Lee et al., 2013). These findings highlight the importance of minimizing the potential effects of aerobic exercise when evaluating the specific influence of resistance exercise on CNS activity.

In addition to BDNF, several studies have examined the effects of resistance exercise on insulin-like growth factor 1 (IGF-1). IGF-1 is a hormone structurally similar to insulin with demonstrated roles in cognitive, neuroendocrine, and hippocampal function (Aberg et al., 2006; Daftary and Gore, 2005; van Dam et al., 2000). Ladder climbing provided over an 8-week period increases serum and hippocampal concentrations of IGF-1, and increases IGF-1 receptor density in the hippocampus (Cassilhas et al., 2012a; Cassilhas et al., 2012b). Notably, aerobic exercise only produces changes in hippocampal IGF-1 and not IGF-1 receptor density, indicating that the latter effect may be selective to resistance modalities. These effects were not reported in a later study that used an acute training procedure (Fernandes et al. 2016), suggesting that the effects of resistance exercise on IGF-1 might differ between acute and chronic regimens. Interestingly, significant and positive correlations were observed following chronic training between systemic and hippocampal IGF-1 concentrations, as well as performance in a passive avoidance task (Cassilhas et al., 2012b). Muscle hypertrophy in response to resistance exercise is regulated by IGF-1, and numerous studies have revealed upregulation of this protein within muscle tissue in response to resistance training (see reviews by Adamo and Farrar, 2006; Adams, 2002). In addition, IGF-1 has blood-brain-barrier (BBB) permeability, and previous studies have demonstrated increased transport of circulating IGF-1 across the BBB in response to exercise (Carro et al., 2000; Nishijima et al., 2010). As a consequence, IGF-1 originating from skeletal muscle might provide a signaling mechanism for the centrally mediated action of resistance exercise and its cognitive-enhancing effects.

4.4 Drug Use and BDNF

Epidemiological studies have consistently indicated that regular engagement in exercise is associated with lower rates of drug use (e.g., Field et al. 2001; Korhonen et al., 2009; Strohle et al., 2007). The effects of exercise on measures of drug use have traditionally been studied in the animal laboratory using exclusively aerobic procedures (e.g., wheel running). These studies have typically supported the human literature and revealed protective effects of aerobic training on measures of drug-seeking and drug-taking behavior (see reviews by Lynch et al., 2013; Smith and Lynch, 2012). Recently, we evaluated the effects of a ladder-climbing procedure (see Section 3.2) on cocaine self-administration in laboratory rats (Strickland et al., 2016). Exercising rats in that study self-administered significantly less cocaine than sedentary subjects receiving equal handling and exposure to the ladder apparatus without resistance climbing. In that study, we also investigated the effects of resistance training on BDNF mRNA expression in the nucleus accumbens, a brain region that regulates reward and reinforcement and is implicated in drug use. Whereas the neurobiological effects underlying the influence of aerobic exercise on drug use have been well characterized (see reviews by Lynch et al., 2013; Morgan et al., 2015), the systems

related to resistance training have received little attention. We found that resistance training provided prior to and during cocaine exposure produced reductions in BDNF mRNA expression in the nucleus accumbens core (Strickland et al., 2016). Cocaine exposure and withdrawal increases BDNF expression in the nucleus accumbens, which may influence the development of dysregulated patterns of drug intake characteristic of substance use disorders (see review by Li and Wolf, 2015). Wheel running in rodents normalizes cocaine-induced changes in BDNF, which may in turn mediate the protective effects of aerobic exercise on cocaine self-administration (Peterson et al., 2014). Our findings with resistance training suggest that alterations in cocaine-induced BDNF expression may also underlie the effects of resistance exercise on drug intake. Future studies are needed to evaluate the relationship between changes in drug self-administration and alterations in dopamine, opioid, and endocannabinoid-mediated mechanisms of drug reinforcement, given the demonstrated effects of resistance training on these neurobiological systems in other research domains (see Section 4.1).

5. Future Directions and Conclusions

Numerous models of resistance exercise are currently used in laboratory animals, and these procedures have been important in determining the peripheral effects of strength training and its role in muscle hypertrophy and growth (Bodine, 2006; Hortobagyi and Maffiuletti, 2011). Although less is known about the neurobiological effects of resistance relative to aerobic exercise, the available evidence from several different research domains provides some insight and indicates several areas where CNS activity may differ between the two exercise modalities. Based on the relative advantages and disadvantages of each resistance model, it is our opinion that whole organism procedures that (1) limit the use of potentially noxious stimuli and (2) minimize the contribution of aerobic factors are best suited for the purpose of studying CNS activity. Whole organism models evoke activity from the subject in a holistic manner rather than an isolated muscle region and thus more closely model human resistance training. Noxious stimuli, such as electric shock or complete water submersion, introduce stress-related confounding factors that complicate the examination of resistance exercise on CNS function. Similarly, models with significant aerobic components make it difficult to isolate the effects contributed by the resistance manipulation. Understanding the limitations of resistance exercise models will provide researchers the information necessary to design future studies that elucidate the effects of resistance exercise on CNS structure and function.

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Highlights

- We describe and evaluate available animal models of resistance exercise
- Animal models provide advantages for understanding neurobiological effects
- These models have evaluated effects on pain, anxiety, memory, and drug use
- Models that limit noxious stimuli and aerobic exercise are key for future research

Table 1

Advantages and Disadvantages of Animal Models of Resistance Exercise for CNS Studies

	Model	Advantages	Disadvantages
In Situ	Electrical Stimulation	Targeted control of muscle stimulation. Opposite leg serves as internal control for natural growth.	Repeated use of anesthesia and stressful stimuli. Limited face validity.
	Chronic Stretch	Opposite leg serves as internal control for natural growth.	Chronic rather than intermittent muscle stimulation. Limited face validity.
	Compensatory Overload	Opposite leg serves as internal control for natural growth. Rapid muscle growth.	Immunological responses due to surgery. Limited face validity.
Whole Organism	Ladder Climb	Minimizes the need for stress and aversive stimuli to maintain behavior.	Primarily a hindlimb model of resistance training.
	Resistance Wheel Running	Limited aerobic components to exercise. Voluntary procedure. Variability in exercise output can be used for correlational analyses.	Significant aerobic components to exercise.
	Squat Exercise	Similarity to human resistance training in modality, time course of muscle growth, and hypertrophic outcomes. Limited aerobic components to exercise.	Use of stress through electrical shock and other noxious stimuli to maintain behavior.
	Flywheel	Can be applied to hindlimb suspension studies to study long-term muscle disuse.	Limited generalizability in instances other than long- term muscle disuse (e.g., paralysis).
	Water-Based Exercise	Unique model of frequently used modality of human resistance exercise.	Stressful stimuli, such as total water submersion, may confound results. Some aerobic components to exercise.

Table 2

Studies Examining Central Mechanisms of Resistance Exercise in Animal Models

	Study	Resistance Model	Comparison Groups	Principle Finding(s)
Antinociception	Galdino et al., 2010	Squat	Sedentary	Antinociception following acute resistance exercise. Antinociception reversed by subcutaneous naloxone.
	de Souza et al., 2013	Squat	Sedentary	Antinociception following acute resistance exercise. Antinociception reversed by systemic but not central injection of adrenergic receptor antagonists.
	Galdino et al., 2014a	Squat	Sedentary	Antinociception following acute resistance exercise.
	Galdino et al., 2014b	Squat	Sedentary (Sham Stimulation)	Antinociception following acute resistance exercise. Antinociception reversed by systemic and central CB_1 and CB_2 inverse agonists and potentiated by reuptake and metabolic inhibitors. Upregulation of CB1 receptors.
Anxiety & HPA Axis	Ebal et al., 2007	Modified Ladder Climb	Sedentary	Increased corticosterone in resistance trained subjects.
	Lipari et al., 2010	Ladder Climb (Chronic)	Sedentary	Increased vasopressin-positive neurons in the hypothalamic SON after 45 days of resistance training.
	Farina et al., 2014	Ladder Climb (Chronic)	Sedentary	Increased vasopressin-positive neurons in the hypothalamic PVN 15 days after the cessation of training. Decreased oxytocin-positive neurons in the hypothalamic PVN during resistance training.
	Aparicio et al., 2014	Resistance Treadmill	Sedentary	Increased corticosterone in resistance trained subjects. Increased quadricep nitrogen content.
Memory	Lee et al., 2012	Resistance Wheel	Sedentary; Running Wheel	Improved performance on a Morris water maze task. Increased hippocampal BDNF and drownstream effectors TrkB, CREB, PKA, PKC, and MAPK. Increased plantaris mass.
	Cassilhas et al., 2012a	Ladder Climb (Chronic)	Sedentary; Sham (Apparatus); Treadmill Run	Improved performance in a Morris water maze task. No change in hippocampal BDNF with resistance exercise. Upregulation of hippocampal IGF-1 and receptor density.
	Cassilhas et al., 2012b	Ladder Climb (Chronic)	Sedentary; Sham (Apparatus)	Increased conditioning on a passive avoidance task. Upregulation of systemic and hippocampal IGF-1. Performance on the passive avoidance task was correlated with IGF-1 concentration. Increased muscle fiber area.
	Lee et al., 2013	Resistance Wheel	Sedentary; Running Wheel	Increased hippocampal neurogenesis. No change in soleus or plantaris mass.
	Suijo et al., 2013	Resistance Wheel	Sedentary; Running Wheel	Improved performance on a Morris water maze task. Upregulation of hippocampal BDNF and CREB. Increased plantaris mass.
	Gomes et al., 2014	Ladder Climb (Chronic)	Sham (Apparatus)	Increased hippocampal cell proliferation and anti-apoptotic protein immunoreactivity.
	Fernandes et al., 2016	Ladder Climb (Acute)	Sedentary	Increased contextual (but not auditory) fear conditioning. No change in hippocampal IGF-1 expression. Increased synaptic protein expression (e.g., synapsin).
	Kim et al., 2016	Combined Treadmill Training & Ladder Climb	Sedentary	Improved performance on a Morris water maze task and increased avoidance conditioning. Increased hippocampal BDNF expression.
	Nokia et al., 2016	Ladder Climb (Chronic)	Sedentary; Treadmill Run	No change in hippocampal neurogenesis with resistance training.

	Study	Resistance Model	Comparison Groups	Principle Finding(s)
Drug Self-Administration	Strickland et al., 2016	Ladder Climb	Sham (Apparatus)	Decreased cocaine self-administration. Decreased BDNF mRNA in the nucleus accumbens core. Increased gastrocnemius mass.

Note. SON = supraopitic nucleus; PVN = paraventricular nucleus; BDNF = brain-derived neurotrophic factor; IGF-1 = insulin-like growth factor; Sham (Apparatus) = Sedentary group with equal exposure to the apparatus.