Journal of Neuroscience Methods 273 (2016) 191–200

Contents lists available at ScienceDirect

Journal of Neuroscience Methods

journal homepage: www.elsevier.com/locate/jneumeth

# Animal models of resistance exercise and their application to neuroscience research

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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.

## ARTICLE INFO

*Article history:*
Received 17 May 2016
Received in revised form 24 July 2016
Accepted 3 August 2016
Available online 4 August 2016

*Keywords:*
Cognition
Mental health
Neurobiology
Resistance training
Rodent
Strength training

## 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.

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http://dx.doi.org/10.1016/j.jneumeth.2016.08.003
0165-0270/

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## 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