Journal of Neuroscience Methods 212 (2013) 338–343

Contents lists available at SciVerse ScienceDirect

Journal of Neuroscience Methods

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

Basic Neuroscience

Novel technology for modulating locomotor activity as an operant response in the mouse: Implications for neuroscience studies involving "exercise" in rodents

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HIGHLIGHTS

- We have developed a novel, low-cost technology to monitor and modulate locomotor activity in murine subjects.
- These devices can be used to establish locomotor activity as an operant response reinforced by food pellet presentations.
- Using this technology, schedules of reinforcement can reliably modulate motor activity.
- These devices may be used to study various effects of physical exercise, psychomotor sensitization, and drug addiction.

ARTICLE INFO

Article history:
Received 13 September 2012
Received in revised form 26 October 2012
Accepted 30 October 2012

Keywords:
Locomotor activity
Operant behavior
Positive reinforcement
Schedule of reinforcement
Exercise
Mouse
Running wheel
Treadmill

ABSTRACT

We have developed a novel, low-cost device designed to monitor and modulate locomotor activity in murine subjects. This technology has immediate application to the study of effects of physical exercise on various neurobiological endpoints, and will also likely be useful in the study of psychomotor sensitization and drug addiction. Here we demonstrate the capacity of these devices to establish locomotor activity as an operant response reinforced by food pellet presentations, and show that schedules of reinforcement can reliably control this behavior. Importantly, these data show that varying degrees of increased locomotor activity (in other words, "exercise") can be elicited and maintained in mice by manipulating the schedule of reinforcement. Our findings argue that the present technology might reduce the imposition of stress and motivational bias inherent in more traditional procedures for establishing exercise in laboratory rodents, while allowing for true random assignment to experimental groups. As interest in physical exercise as a modulating factor in numerous clinical conditions continues to grow, technologies like the one proposed here are likely to become critical in conducting future experiments along these lines.

1. Introduction

In recent years, preclinical research has increasingly focused on the effects of physical exercise on a range of neurobiological endpoints, including sensitivity to drugs of abuse (Cosgrove et al., 2002; Larson and Carroll, 2005; Smith et al., 2008a,b; Kanarek et al., 2009; Zlebnik et al., 2010), depression (Bjørnebekk et al., 2006; Zheng et al., 2006; Ernst et al., 2006; Greenwood et al., 2007; Duman et al., 2008), expression of neurotrophic factors (Neeper et al., 1996; Bjørnebekk et al., 2005; Aberg et al., 2008), cognition and hippocampal plasticity in aging (Wolf et al., 2006; Nichol et al., 2007; Parachikova et al., 2008; Pietropaolo et al., 2008), and recovery after ischemia and stroke (Marin et al., 2003; Luo et al., 2007; Ploughman et al., 2007). Essentially all of these studies have used laboratory rodents, and engendered high levels of physical activity through the use of running wheels or treadmills. Both of these approaches have specific limitations.

In this regard, the use of freely accessible running wheels has often been described as "voluntary exercise", while automated running wheels or treadmills are typically referred to as "forced exercise". Studies have documented important differences in outcomes elicited by "voluntary" versus "forced" exercise (Leasure and Jones, 2008). Subjecting rodents to automated treadmill activity induces significant stress responses manifested as increased plasma corticosterone (Coleman et al., 1998), up-regulation of mitogen activated protein kinases in skeletal muscle (Nakamura et al., 2005), damage to intestinal musculature (Rosa et al., 2008) and increased susceptibility to influenza infection (Murphy et al., 2008). There are inherent motivational factors associated with

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http://dx.doi.org/10.1016/j.jneumeth.2012.10.020

"forced" exercise as well, such that mice placed in a wheel that is already rotating will operate a switch to stop it, although if the wheel is stopped by the experimenter, subjects will operate another switch to start it rotating again (Kavanau, 1963, 1967). Thus, using "forced exercise" to establish physical activity introduces significant stress and motivational effects which may represent an unavoidable confound to the endpoint of interest – particularly in regards to drug abuse (Goeders, 2003; Koob, 2008; Sinha, 2008). Similarly, the use of freely accessible running wheels often eliminates true random assignment to experimental groups, as inter-subject variability in wheel running activity is high. Thus, many studies employing this approach to establish physical exercise must resort to a median split, or simply drop animals failing to achieve some post hoc minimum level of activity.

Somewhat related to this later point, it is important to note that the opportunity to engage in wheel running itself functions as a reinforcer, as rodents will engage in operant behaviors maintained by the temporary unlocking of a wheel (Kagan and Berkun, 1954; Collier and Hirsch, 1971; Collier et al., 1990; Iversen, 1993; Belke, 1997; Belke and Wagner, 2005), by the temporary operation of a motorized wheel (Kavanau, 1963, 1967) or by access to an area containing a wheel (Collier et al., 1989; Sherwin, 1996; Sherwin and Nicol, 1996), which may confound the findings of studies combining this form of exercise with the opportunity to sample other reinforcers (e.g., drugs of abuse, food pellets, electrical brain stimulation). Thus, any differences observed between the reinforcing effects of a stimulus in animals with or without a wheel running history may potentially be unrelated to exercise-induced physiological changes and instead related to behavioral variables involving the choice between the motivational effects of one stimulus (wheel running) and another (a drug). Indeed, a common feature of so-called "enriched environments" is free access to a running wheel (Solinas et al., 2008), confounding any effects of exercise with those of environmental enrichment.

The methodological challenges presented by these two most common animal models of exercise, running wheels and treadmills, are disappointing as they limit the validity of experimental approaches to investigate the potentially important roles of physical exercise against a range of endpoints of interest. It seems clear that the development of an animal model of physical exercise, which could avoid the imposition of stress and motivational bias inherent in the current techniques, and allow for true random assignment to experimental groups, would greatly benefit our ability to assess the effects of exercise on brain and behavior. Wheel-running activity has previously been demonstrated to come under operant control when food presentation was contingent on this behavior (Skinner and Morse, 1958), and here we elaborate on that model to establish spontaneous locomotor activity within the home cage as an operant response in the mouse.

2. Methods

2.1. Animals

All studies were carried out in accordance with the Guide for Care and Use of Laboratory Animals as adopted and promulgated by the National Institutes of Health. Experimental protocols were approved by the Institutional Animal Care and Use Committee at the University of Arkansas for Medical Sciences. All experiments were conducted in adult male NIH Swiss mice housed in an Association for Assessment and Accreditation of Laboratory Animal Care (AAALAC) accredited animal facility. Mice were maintained on an inverted light:dark cycle (lights on at 1900 h, off at 0700 h) to facilitate conduct of behavioral studies during the most active phase of the subjects' circadian cycle.

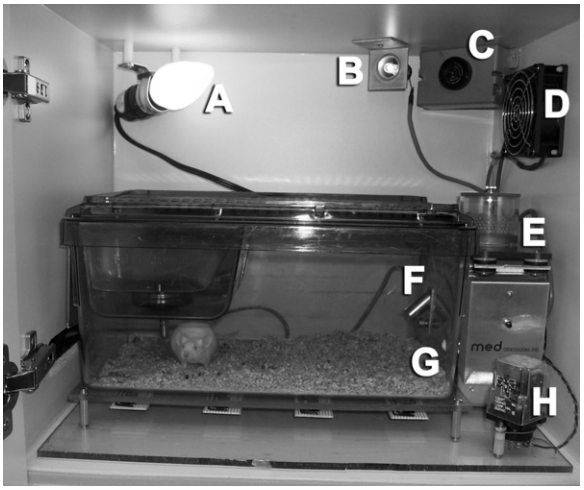

Fig. 1. Photo of the equipment used to establish locomotor activity as an operant response in mice. (A) Chamber light to establish the photoperiod, (B) house light, (C) tone generator, (D) exhaust fan, (E) pellet dispenser, (F) chute to direct pellets into the cage, (G) stimulus light, (H) audible feedback relay. (Note that since experiments were conducted during the subjective dark phase, the house light and stimulus light were only illuminated when the chamber light was off.) Further information is presented in Section 2.3 of the text.

2.2. Surgical methods

All subjects were surgically implanted with 1 cm diameter, 0.3 cm thick disc-shaped neodymium magnets (K&J Magnetics, Inc., Jamison, PA, USA) for the duration of the study. The small magnets were sealed in Parafilm and gas-sterilized prior to implantation. Following appropriate anesthetia using ketamine (100 mg/kg, i.p.) and xylazine (10 mg/kg, i.p.), the abdominal area of each mouse was shaved and sanitized with iodine swabs. Mice were positioned on a clean Plexiglas surgical surface using silastic restraint cuffs around the limbs. A rostral-caudal cut approximately 1.0 cm in length was made approximately 1.5 cm off the midline using skin scissors. A small subcutaneous pocket was then created across the midline via blunt dissection of the underlying fascia with curved microforceps. The sterilized magnet was inserted into the subcutaneous pocket using non-magnetic titanium forceps, and the incision was closed using absorbable suture material. Surgeries were performed at least 7 days before initiation of experiments. Following surgery, mice were individually housed in Lab Products, Inc. Super Mouse 750^{TM} Micro-Isolator^{TM} cages (floor area: >483 cm^2, cage dimensions 32.7 cm × 19.0 cm × 14.3 cm) placed atop customized platforms within light- and sound-attenuating chambers (see below).

2.3. Apparatus

We have developed novel experimental chambers to assess and control ambulatory behavior in murine subjects (Fig. 1). Briefly, these chambers utilize an array of 16 Hall-effect switches (Digi-Key Corporation, Thief River Falls, MN, USA) mounted to a platform which fits beneath each subject's cage. The Hall effect refers to the potential voltage difference across a thin sheet of conducting or semiconducting material through which an electric current is flowing; such current is momentarily created by a magnetic field applied perpendicular to the Hall element. The surgically implanted magnets described above thus allow subjects to activate the switches beneath their cages as they ambulate over them. Hall effect sensors are readily available from a variety of different manufacturers, and are widely used in various applications, such as fluid flow sensors, power sensors, and pressure sensors. Hall effect devices produce a