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Research article

Adaptation to a blood pressure telemetry system revealed by measures of activity, agility and operant learning in mice

Anfisa Popova [a,b], Darya Tsvirkun [c,f], Oleg Dolgov [d], Konstantin Anokhin [d], Jeffrey Alberts [e], Evgeniia Lagereva [a], Marc-Antoine Custaud [f,g], Guillemette Gauquelin-Koch [h], Olga Vinogradova [a], Alexander Andreev-Andrievskiy [a,b,*]

[a] Institute for Biomedical Problems, Russian Academy of Sciences, Khoroshevskoe Shosse, 76A, Moscow, 123007, Russia
[b] Moscow State University, Biology Faculty, Leninskie Gory, 1/12, Moscow, 119234, Russia
[c] Research Center for Obstetrics, Gynecology and Parinatology, Ministry of Healthcare of the Russian Federation, Oparina Street, 4, Moscow, 117997, Russia
[d] National Research Centre "Kurchatov Institute", pl. Akademika Kurchatova, 1, Moscow, 123098, Russia
[e] Department of Psychological and Brain Sciences, Indiana University, Bloomington, IN 47405, USA
[f] Laboratory of Integrated Neurovascular and Mitochondrial Biology (BNMI), UMR CNRS 6214, INSERM 1083, Angers, France
[g] CaDyWEC International Laboratory, Angers University, 49045 Angers CEDEX 01, France
[h] Centre National d'Etudes Spatiales, 2 Place Maurice Quentin, 75 039 Paris CEDEX 01, France

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ABSTRACT

Introduction: Implantable telemetry enables continuous monitoring of physiological functions in freely moving animals and can greatly complement pharmacological research. Despite its miniaturization, a sensor/transmitter constitutes 5% or more of a mouse's bodyweight. The aim of the present study was to evaluate whether factors related to the presence of a probe/transmitter influence the ambulatory activity, strength, agility, or operant, motivated behaviors of this small rodent.
Methods: Adult male mice (C57BL/6 N, 22–25 g, 9–10 weeks; implanted n = 26, intact n = 45) were evaluated during week-long tests, conducted three and eight weeks after surgical implantation of the PA-C10 blood pressure probe. An open field test, grip force measurement, Rotarod test were performed, followed by 7-day continuous monitoring of spontaneous wheel running activity and positively reinforced operant conditioning in an automated data collection system.
Results: An implanted blood pressure transmitter did not affect behavior of mice in the open field test, on the Rotarod or their grip force, compared to unoperated controls. Voluntary wheel running distance was reduced three, but not eight weeks after implantation. Three weeks after the surgery, performance in the positively reinforced operant conditioning in operated mice was slightly decreased compared to intact animals, while retention and acquisition of a 2nd, reversal-learning task eight weeks after the surgery were unaffected.
Discussion: We conclude that an implantable transmitter may have detectable effects in the first few weeks following implantation on some elements of mouse behavior. With sufficient recovery, mice perform comparably to unoperated controls in tests of strength, endurance, agility and learned operant behavior.

1. Introduction

A scientific understanding of animal behavior usually includes observation, description, and measurement of movements under undisturbed conditions as well as in controlled settings in which environmental conditions and events can be systematically manipulated. Ideally, concomitant physiological processes (e.g., heart rate, blood pressure, temperature, neural and muscular activity) are also part of such studies, for these measures can powerfully augment the interpretation of behavior (and vice versa).

Implanted sensors have long been used to monitor and record physiological processes in animal subjects, but the connectors and wires used to attach to external equipment limit the range of applications and often interfere with behavior. The advent and development of implantable telemetry, however, has vastly expanded the applicability of physiological measures of unrestrained, behaving animals (Kramer & Kinter, 2003; Kurtz et al., 2005). Telemetry is now used in unrestrained, free-moving animals to monitor autonomic functions including heart rate, blood pressure or body temperature during stressful situations (Depino & Gross, 2006; van Bogaert et al., 2006), exercise (Adlam et

* Corresponding author at: Institute for Biomedical Problems, Russian Academy of Sciences, Khoroshevskoe shosse, 76A, Moscow 123007, Russia.
E-mail address: aandrievsky@gmail.com (A. Andreev-Andrievskiy).

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al., 2011), avoidance testing (Wan, Diamant, De Jong, & de Wied, 1990; Zhang, Murphy, & Feldon, 2004), to record muscle (Langenbach, van Ruijven, & van Eijden, 2002) and brain (Tang, Orchard, & Sanford, 2002) activity in rats, mice and guinea pigs (Schmitz, Henke, Tacke, & Guth, 2016) as well as other species.

A major, general advantage of telemetric methods is that they allow long-term recordings from freely moving animals in a variety of environments. There are no connectors or wires to constrain animals or their social interactions. Moreover, in many situations, such as investigations of potential "stress effects", investigators have relied on samples of blood or urine at single time points. At best, such measures represent a limited timeframe of condensed information. In contrast, telemetered data can be measured continuously and in greater detail. In all, telemetric methods are recognized for improved scientific yield as well as the promotion of animal welfare during experimentation (Morton et al., 2003).

As with any technique, the limitations of telemetric methods must be considered. Specifically, we must evaluate the applicability of telemetric methods to mice, a species that has become vital to many specialties, due primarily to knowledge of its genotype and the availability of numerous genetically-engineered strains. Telemetric implants have been miniaturized, but due to a mouse's diminutive size, they still represent about 5–7% of its body mass. Whether inserted subcutaneously or intraperitoneally, it is prudent to evaluate possible interference with general activity and motor patterns specific to research questions. Indeed, some say such limitations cannot be avoided (Braga & Burmeister, 2011; Baumans, Bouwknecht, & Boere, 2001; Helwig, Ward, Blaha, & Leon, 2012; Kaïdi et al., 2007). In addition, monitoring blood pressure in mice with implantable telemetry usually requires ligation of a carotid artery, which could negatively affect circulation to the brain and thus alter behavior (Kaïdi et al., 2007; Kurtz et al., 2005). Again, assessment is important. Finally, basic animal welfare should be considered in relation to implantable telemetry probes. There have been welfare assessments based on mouse bodyweight and activity (Baumans et al., 2001; Helwig et al., 2012; Johnston et al., 2007; Leon, 2004), but less is known about the long-term consequences of probes for ambulatory activity and learning and the potential interference of the implant with the experimental data.

The aim of the present study was to investigate the impact of an implantable blood pressure sensor on the performance of mice in a variety of tests involving motoric strength, coordination, activity, as well as a task of motivated learning and memory. Specifically, we measured in implanted mice and control mice, grip strength, Rotarod performance, voluntary wheel running and the acquisition and retention of positively reinforced operant tasks.

2. Materials and methods

2.1. Ethical statement

The data for this study were collected previously in two experiments approved by Bioethics commission of Moscow State University Institute of Mitoengineering (Protocol No 35, 1 November 2012) and by the Biomedical Ethics Commission of Institute for biomedical problems of the Russian academy of sciences (protocol No 319, 4 April 2013) and conducted in compliance with the European Convention for the Protection of Vertebrate Animals used for Experimental and Other Scientific Purposes (Directive 63/EU, 2010).

2.2. Study overview

Adult male mice were evaluated during week-long tests, conducted three and eight weeks after surgical implantation of the PA-C10 (Data Sciences International, USA) blood pressure probe. Performance was compared to intact (unoperated) control subjects, tested identically.

On the morning of day 0 of each test session, an open field test was performed, followed by grip force measurement and the Rotarod test. On the evening of the same day, animals were individually housed in Phenomaster (TSE Instruments, Germany) cages, an automated data collection system, and monitored continuously for 7 days. We used the Phenomaster to measure unrestricted, spontaneous wheel running activity; the Phenomaster's "operant wall" was programmed to provide sessions of positively reinforced operant conditioning. The testing regime was repeated five weeks later. During behavioral monitoring and testing mice were housed individually; they were socially housed throughout the rest of the study.

The data were collected during two separate experiments in support of the BION-M1 biosatellite project (Andreev-Andrievskiy et al., 2014b; Sychev et al., 2014). The first replicate (10 implanted and 20 intact mice) was conducted November–December 2012 and the second replicate (16 implanted and 25 intact mice) was run March–August 2013, following the same design.

2.3. Animals

Male C57BL/6 N mice (n = 71) weighing 22–25 g and 9–10 weeks old were purchased from the Animal Breeding Facility - Branch of Shemyakin & Ovchinnikov Institute of Bioorganic Chemistry. Mice were specific pathogen free.

2.4. Housing

Mice were housed at 20–26 °C, 30–70% relative humidity and 12-h light-dark cycle (lights on at 09:00) in individually ventilated cages (GM500, Tecniplast, Italy). Pelleted chow (Assortiment-Agro, Russia) and water were provided ad libitum except for the periods of operant conditioning, when access to food was restricted to induce 10–15% body weight loss.

During post-surgery recovery (5–6 days) implanted mice were housed individually. Otherwise, mice were kept in groups of three (one implanted animal and 2 intact cohabitants). Red plastic nesting chambers and nesting material were provided for the environment enrichment. Mice lived individually during week-long testing in the Phenomaster cages.

2.5. Telemetry probes implantation

Three weeks before the start of experimentation, miniature probes for blood pressure monitoring (model PA-C10) weighing 1.4 g were implanted according to the manufacturer's instructions (Huetteman & Bogie, 2009). The catheter of the probe was implanted into the left carotid so that its tip just reached the aorta under on-line blood pressure waveform control. The body of the transmitter was implanted subcutaneously in the flank, as described next.

Mice were anaesthetized with tiletamine, zolazepam (15 mg/kg each) and xylazine (3 mg/kg) in solution injected intraperitoneally in a volume of 10 ml/kg. Depth of anesthesia was assessed regularly by hind leg pinch and observation of respiration rate; additional dose(s) of the mixture (about 20% of the initial dose) was administered, as needed. A midline incision was made on the ventral neck. The left common carotid artery was separated and ligated 1–2 mm cranially to its bifurcation. A second ligature was used to suspend the artery 4–5 mm proximal to the site of ligation. Through a small incision in the artery wall, the catheter was advanced 6–7 mm towards the aorta and fixed in place with sutures and acrylic glue. A subcutaneous pocket on the flank of the animal was made with blunt scissors, and the transmitter was inserted therein using a small hemostat. The catheter and the transmitter were fixed in place with acrylic glue and the skin incision closed with absorbable sutures. During the recovery period, mice were under daily veterinarian observation and received ibuprofen 4 mg/ml and Bactrim 4 mg/ml in drinking water. Bodyweight was monitored daily