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Journal of Pharmacological and Toxicological Methods 53 (2006) 117 – 127

Journal of Pharmacological and Toxicological Methods

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How to

How to achieve chronic intravenous drug self-administration in mice

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Received 6 October 2004; accepted 15 March 2005

Abstract

Introduction: Self-administration, the best animal model of drug addiction, requires implantation of indwelling jugular catheters. Surgical procedures in mice, the most common species for transgenic modeling, are difficult owing to size and scale. The goal of this paper was to describe how to achieve successful intravenous drug self-administration in mice. **Method:** The surgical and self-administration training procedures developed for rats and other species have been adopted for mice and described in a step-by-step manner with reference to sources for equipment, materials, and parts. **Results:** The method can be used for studying self-administration behavior in freely moving mice up to 4 weeks. The relatively quick loss of catheter patency was due to growth of neointima tissue. **Discussion:** Drug self-administration is achievable in mice, and the model is limited only by eventual loss of catheter patency, a process probably triggered by mechanical damage of the endothelium, by the effect of drug injections, or a combination of these factors.

Keywords: Drugs of abuse; Indwelling catheter; Jugular vein; Methods; Mice; Self-administration; Surgical procedure

1. Introduction

The best-characterized and most commonly used vertebrate organism for transgenic and related model studies is the mouse. There are a variety of genetic tools generated for mice allowing the creation of a virtually unlimited number of inbred strains with desirable mutations. The "use of these animals would make available the large number of readily obtainable inbred strains facilitating the genetic analysis of chronic drug effects." This is a quote from one of the first publications on technique for the chronic jugular vein cannulation in mice (Barr, Holmes, Ryan, & Sharpless, 1979). However, it took 16 years before the first study comparing self-administration in two different strains of mice was published (Grahame & Cunningham, 1995).

Self-administration procedure is one of the most relevant behavioral models of drug addiction. Most drugs abused by humans are self-administered by animals. The procedure of self-administration is widely used in rats and monkeys. The total number of articles on intravenous drug self-administration in which rats or monkeys served as subjects is approximately 1200 and 560, respectively. Mice have been used for the same purpose in approximately only 80 studies to date (as of January 2005). However, in only half of those studies were chronic jugular catheters used for self-administration, constituting approximately 2.2% of all intravenous self-administration studies in animals (Tsibulsky, 2005). There are several reasons why rats have been used 15-fold more frequently than mice. The main reason is quite obvious: rats have approximately 15-fold larger body size than mice. Undoubtedly, animal size is an important factor with regard to the greater complexity of surgical procedures and catheter patency maintenance in smaller animals.

There are two different methods of intravenous self-administration in mice. The first is similar to the method of indwelling venous cannulae in freely moving animals developed by Sharpless (1959) for cats and Popovic and

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doi:10.1016/j.vascn.2005.03.009

Popovic (1960) for rats and mice (Popovic, Sybers & Popovic, 1968). Weeks (1962) was the first to use this method for morphine self-administration in rats. Almost thirty years later, Carney, Landrum, Cheng, and Seale (1991) adapted the method for mice. Their method involves exposure of the right external jugular vein under anesthesia, followed by insertion of a silicone or polyethylene cannula that is secured by means of a ligature placed around the vein. The tubing is tunneled under the skin to a connector fixed on the back or on the head of the animal. With this chronic catheterization method, different manipulandae can be used for self-administration: lever-presses, nose-pokes, chain pulling, runway, tail movements etc. The use of this technique allows the investigator to compare the results in mice directly with results obtained in more than two thousand studies on drug self-administration conducted in rats, monkeys, dogs etc.

The second method of cannulation was developed specifically for mice by Plager (1972), a method modified by Moran and Straus (1980) and used for self-administration of morphine in mice by Criswell (1982, Criswell and Ridings, 1983). According to this method, the intact mouse is placed into an experimental chamber with a hole for nose-poke. The entire tail is extended outside through a smaller hole in the opposite wall and fixed with adhesive tape to the floor, causing the mouse to be substantially restrained. The stainless steel cannula is inserted into the lateral tail vein and connected to the syringe pump. Usually, each mouse is used for one or a few sessions. Restraining limits the range of possible manipulandae to the nose-poke response only, and the vein often ruptures in several sessions. Additional control groups of mice, a group receiving saline injections contingent upon their activity and a yoked control group receiving the same drug simultaneously with the experimental group regardless of their own activity, are required to proof that acquired typically within the first session behavior is due to drug's reinforcing effect (Criswell & Ridings, 1983; Kuzmin, Zvartau, Gessa, Martellotta, & Fratta, 1992).

It is clear that the advantage of the indwelling catheter method is that animals can more freely display the entire repertoire of behavior for many weeks or even months. The advantage of the tail vein cannulation method is that the experimenter can use a larger number of animals because there is no complicated surgical procedure (insertion of the needle into the vein can typically be accomplished in one or two attempts). However, in our opinion, the higher animal usage per short-term experiment of this latter method is a poor substitute for conducting a long-term study with a few animals. The goal of the present study was to select the best materials and procedures and provide researchers with a step-by-step description of the indwelling intravenous catheter technique for self-administration or other behavioral studies in freely moving mice. The excellent description of the procedure for rats provided by Caine, Lintz, and Koobm (1993) that was subsequently adapted for mice (briefly described in Deroche et al., 1997), was used as a starting point for our initial work (Tsibulsky & Norman, 2001). The method described herein represents a thorough compilation of the best achievements of manufacturers and other researchers as well as our own studies on making the mouse self-administration technique feasible. A similar, although more general, description was published recently about self-administration in rats (Xi & Stein, 2003). The procedure for mice is still technically difficult and should only be attempted by those with relevant surgical experience on larger animals.

2. Methods

2.1. Subjects and materials

2.1.1. Subjects

Male Swiss Webster mice (Charles River Laboratories, MA, 19–21 g body weight) were housed with 4 animals per standard acrylic cage (26 × 15 × 11 cm) with metal grid lids and air filter tops. After surgery, mice were housed individually because of their natural habit to gnaw on each other's guide cannulae. Food and water were available ad libitum. The colony room was maintained on a 12:12 h light/dark cycle (fluorescent lights on at 06:00 hours), at 22 ± 1 °C with a relative humidity of 40 ± 10%. The subjects were allowed to acclimate to environmental conditions for at least 5 days prior to surgery. For all experiments, the Principles of Laboratory Animal Care (NIH publication No. 85-23, revised 1985) were followed and all experimental protocols were approved by IACUC.

2.1.2. Drugs

Cocaine hydrochloride was provided by NIDA (Rockville, MD). Brevital (methohexital sodium) was purchased from Eli Lilly (Indianapolis, IN); ketamine HCl from Abbott Labs (Chicago, IL); midazolam HCl from American Pharmaceutical Partners, Inc. (Schaumburg, IL); streptokinase and polyvinylpyrrolidone (PVP, MW 25,000) from Sigma (St. Louis, MO); timentin (ticarcillin disodium and clavulanate potassium) from SmithKline Beecham (Philadelphia, PA); Flunixin (flunixamine) from Phoenix Scientific, Inc. (St. Joseph, MO).

2.1.3. Intravenous catheter making

2.1.3.1. Parts. Intravenous catheters were assembled from seven individual parts: injection needles; large, medium, and small size tubing; mesh; CO-EX™ tubing and fishing line.

- Injection needles: 25 gauge × 1 in. stainless still injection needle (Becton Dickinson, Franklin Lakes, NJ, www.bd.com, cat. # 301632);